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ADDRESS BY THE VICE-PRESIDENT

Metallic Sutures and Early American Gynecology*

M. PIERCE RUCKER, M.D., RICHMOND, VA.

IT IS well known that Dr. Phillip Syng Physick, the father of American surgery, was not satisfied with the sutures then in use, and that his nephew, John Syng Dorsey, carried on some experiments with absorbable sutures. Whether or not he turned his attention to metallic sutures, I have been unable to learn. At any rate, two of Physick's pupils did some remarkable work with metallic ligatures and sutures. In 1829 Dr. H. S. Levert¹ published his "Experiments on the Use of Metallic Ligatures" in the *American Journal of the Medical Sciences*. Levert ligated the carotid and femoral arteries in dogs with various metallic ligatures and with silk. Around the silk ligatures, collections of pus were invariably found, but the metallic ligatures became "encysted" without producing inflammation. He said that Physick suggested the use of lead, since lead bullets remained in the tissues without causing inflammation, but, so far as Levert knew, no one had actually tried ligatures of this material. About the time that Levert was carrying on his experiments, Dr. J. P. Mettauer, another of Physick's pupils, was actually using lead sutures. The work of Levert was referred to by Bozeman² and Sims,² but seems to have escaped any further notice.

In the anniversary oration of the New York Academy of Medicine in 1858, entitled "Silver Sutures in Surgery," Marion Sims² makes the statement that the silver suture was the greatest surgical discovery of the nineteenth century. He attributes to it his success, and also the founding of the Woman's Hospital of the State of New York. Sims is frequently spoken of as the father of modern

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gynecology. Therefore metallic sutures are the very foundation of the American Gynecological Society. Sims leaves one under the impression that silver sutures are his own invention. The editor⁴ of the *New England Journal of Medicine* says "we can perhaps, after all these years, forgive Sims for his bombastic language, for he richly deserves the credit of perfecting this operation (for vesicovaginal fistula) and of making it clear to the medical profession that the procedure was only consistently successful with the use of the Sims's position, the Sims's speculum, the special needles, and the inlying catheter that he had devised, and, finally, the silver sutures."

I am in complete agreement with this editor, except that there is more to the history of metallic sutures in general and silver sutures in particular than is indicated by either the editor or by Sims. According to Sir James Y. Simpson,⁵ Hippocrates and the ancients used gold and silver wire to hold teeth together in cases of fracture of the jaw. Celsus mentions gold and iron threads only to condemn them for use in animal tissues. The first time that metal was deliberately put into the tissues was in connection with attempts to cure inguinal hernia. Bernard Memis, Franco, Fallopius, and Paré applied what they termed the "golden stitoh" or "golden tie" to the neck of the hernia sac. Aveling⁶ attributes the first use of metallic sutures to *Fabricius ab Aquapendente*. "After describing the ligature of Fallopius which was of thread, and like the ones which we, until lately, have been using, and that of Guido, which was made of metal, and hooked the two lips of the wound together, he says he provided himself with many flexible needles of iron or brass, made soft except at the point, over burning coals. These he passes through the lips of the wound and then turns back the extremities, the right to the left and the left to the right, fitting them over the wound, either straightly and plainly, or by making a knot." Fabricius gives the following reasons for preferring such sutures: (1) Iron does not eat into the flesh. (2) It does not ulcerate out. (3) It does not stretch and break. (4) It is not rotted by the discharge. Aveling was so impressed by the sutures of Fabricius that he had some made for himself, but so far as I know did not report upon their use.

In the eighteenth century Purmann⁵ of Breslau used silver to advantage in wounds of the tongue, and in 1746 Mihles⁵ speaks of using silver and gold threads in the repair of harelip, but Dieffenbach⁵ is credited with being the first modern surgeon to use metallic sutures. In a paper on staphylorrhaphy, published in 1826, he⁷ reported several cases in which he used lead thread to close the defect in the palate. He spoke of the advantage of twisting the wire, over having to tie a knot deep in the oral cavity. It should be remembered that there was no anesthesia in those days. Dieffenbach, being professor of surgery in Berlin, was an important personage, and his article was abstracted in great detail the same year in the *Lancet*.⁸ However, metallic sutures did not become popular in Europe. Gosset⁹ of London used gilded silver wire in a successful vesicovaginal fistula operation in 1833, but there seem to have been no other reports. In fact, Simon¹⁰ of Heidelberg, after adopting Sims' technique in the fifties, went back to fine silk. He said, "I even not only consider it no

progress, but rather disadvantageous, on account of the difficult application and removal of the sutures, and I have not the least doubt that the time is not far distant when the metallic sutures for plastic operations, and especially for that of vesicovaginal fistula, will yield again to the more convenient sutures of fine silk."

It was in America, according to Sir James Y. Simpson,⁵ that the subject of metallic sutures received the greatest attention. In 1827, one year after the publication of Dieffenbach's article on staphylorrhaphy and its abstract in the *Lancet*, Dr. John P. Mettauer¹¹ of Virginia used lead thread in the successful repair of cleft palate. In his paper "On Staphylorrhaphy," published in 1837, he gives Dieffenbach credit for introducing lead sutures. In 1833 he¹² reported a case of ununited parturient laceration of the rectovaginal septum successfully treated with metallic ligatures, and in 1847¹³ seven cases of third degree lacerations of the perineum. Six cases were completely cured. The seventh case was partly relieved and refused a second operation. In 1840¹⁴ he reported the cure of a vesicovaginal fistula, and in 1847¹⁵ he reported a series of six cases. By 1855¹⁶ his series had grown to thirty cases, and he was convinced that every case could be cured. After Sims' report¹⁷ in 1852, the story is well known to everyone.

Dieffenbach, who is looked upon as the author of metallic sutures in Europe, did not recognize their importance, and failed in a field where their use in America attained such remarkable success. He said of vesicovaginal fistula (1836),¹⁸ "I have operated on a woman eighteen times and discharged her unrelieved, I have gathered large rooms full of these unhappy women from all parts of the country, and I have exhausted all resources and have cured but few." Mettauer recognized the value of metallic sutures, and used them not only in staphylorrhaphy but with equal success in perineorrhaphies and vesicovaginal fistula operations. Sims recognized their value and used them in all fields of surgery and convinced the world of their value.

I have been interested to find out the reaction of the general run of the medical profession to these changes in suture material. The files of the *American Journal of the Medical Sciences* serve well for this purpose, for it has been in continuous publication since before sutures were used. Its very first volume¹⁹ contains an abstract from Sir Ashley Cooper's Lectures on Surgery, "Considerable prejudice exists in this country, and we cannot help thinking, with some justice, against the use of sutures." Sir Ashley Cooper, however, says that it is quite a mistake to suppose that sutures are injurious, and that they should never be used, "for a wound often heals better with a suture and a cooling lotion, than with adhesive plaster." Levert's¹ article on metallic ligatures is noted in the references. In 1841 there was an abstract of an article by Thomas Nunneley²⁰ of Leeds recommending threads of caoutchouc for sutures. It is claimed that they can remain much longer without producing irritation of any kind and, being elastic, hold the divided parts in contact and adjust themselves to the swelling of the tissues. Interestingly, the threads were obtained from suspenders, where Marion Sims²¹ said he got his idea for silver

sutures. Other than Mettauer's articles in 1833, 1837, and 1847, there are no more notices of sutures until Sims'¹⁷ classic article in 1852. After that, references to sutures became more frequent. In 1858,³⁰ there is a note that Professor Simpson used platinum wire as being more easily tied than the silver recommended by Dr. Sims. In 1859 Hodge²² has a report of his experiences with annealed iron wire, lead wire and silver wire in various operations. He preferred lead as did Spencer Wells²³ writing in the *Medical Times and Gazette* several years before. In 1859 Emmet²⁴ reported on the use of silver ligatures and sutures in amputation of the breast. In 1863, W. N. Chipperfield²⁵ of Madras is quoted as speaking "favorably of metallic sutures introduced into use by our ingenious countryman, Dr. M. Sims." In India he used iron wire.

Thus we see that the bacteriologic aspect of wound healing was solved by metallic sutures, even before men knew that there were bacteria. When antiseptics and later asepsis began to be practiced, metallic sutures became relatively less important. With Listerism it was possible to use catgut, and Lister²⁸ himself was a great advocate of catgut. The physical properties of catgut were more conducive to easy manipulation. There was another factor in wound healing, the elucidation of which awaited the genius of Halsted.³¹ Halsted³² showed that mass ligatures and sutures caused tissue necrosis, often microscopic in size, but important nevertheless. By tying off individual blood vessels and by closing the wound layer by layer with carefully placed sutures, one got better healing. Fine silk fitted in better with Halsted's meticulous technique, and in the Halsted era metallic sutures practically disappeared.

With improved metallurgic methods, stainless steel wire can now be made as fine as the finest silk. In 1932²⁶ Babcock introduced alloy steel wire for ligatures and sutures. The whole subject has been reopened, and the effect of sutures on wound healing has been restudied with modern methods. It has been found that the tissue reaction as seen under the microscope varies with the kind of suture material²⁹ used. It is greatest with catgut, not so great with silk, much less with cotton, and practically none with metallic sutures. It is interesting to note that these modern investigators confirm the accuracy of the work of Levert and the earlier observations of Fabricius.

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THE HUMAN CONCEPTUS DURING THE FIRST TWO WEEKS OF GESTATION*†

JOHN ROCK, M.D., AND ARTHUR T. HERTIG, M.D., BROOKLINE, MASS.

(From the departments of Gynecology and Pathology, Harvard Medical School, The Fertility Clinic and Pathological Laboratories, Free Hospital for Women, Brookline, The Carnegie Institution of Washington, Department of Embryology, Baltimore)

THE youngest human embryo was conceived, not naturally in the Fallopian tube of its mother, but in a watch glass in the laboratory. It was the last of a series of almost 800 eggs, all recovered from ovarian tissue, of which 138 were exposed by Mrs. Miriam F. Menkin and me to human spermatozoa in about 1 e.e. of Ringer-Locke's solution.^{1, 2} After a pencil drawing was made of this two-cell individual, it was regrettably lost. A few days later, however, another egg similarly treated began its personal existence by changing from a single cell that had been part of the maternal tissue into a two-cell autonomous structure (Fig. 1, A). Because none had been seen to do likewise without spermatozoa, and there were spermatozoa within the zona pellucida, it is probable that this two-cell organism is the result of conjunction of the male and female components. Some weeks later, similar procedures resulted in the production of two ova in the three-cell stage.

Studies of early cleavage stages in the monkey by Lewis and Hartman,³ and in the mouse by Wright and Lewis,⁴ together with ours in the human being, indicate that eggs are fertilized soon after ovulation, usually within twelve hours. The youngest naturally conceived human specimen is one recently found by Hertig.⁵ It consists of eight blastomeres (Fig. 1, B). From the condition of the endometrium and of the corpus luteum, we think it is about 72 hours old. The next oldest human specimen is probably abnormal. It is considered to be 4 days old, and yet consists of only nine cells, several of which have more than one nucleus.

From the meager human material comprising four eggs fertilized in vitro and three‡ segmented ova removed from uteri, we may at present deduce that during the first forty-eight hours following ovulation, the mature egg enters the tube, conjugates therein with the spermatozoon, and achieves segmentation into at least two blastomeres. During the next two days division has progressed to the eight-cell stage, and the egg on the third day may reach the uterine cavity. It does not increase perceptibly in size through the three-cell stage. At the eight-cell stage the unfixed morula is about one-half again as big as the unfertilized ovum.

*Read at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

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‡One additional specimen not illustrated was found to contain about twelve cells and is probably normal.

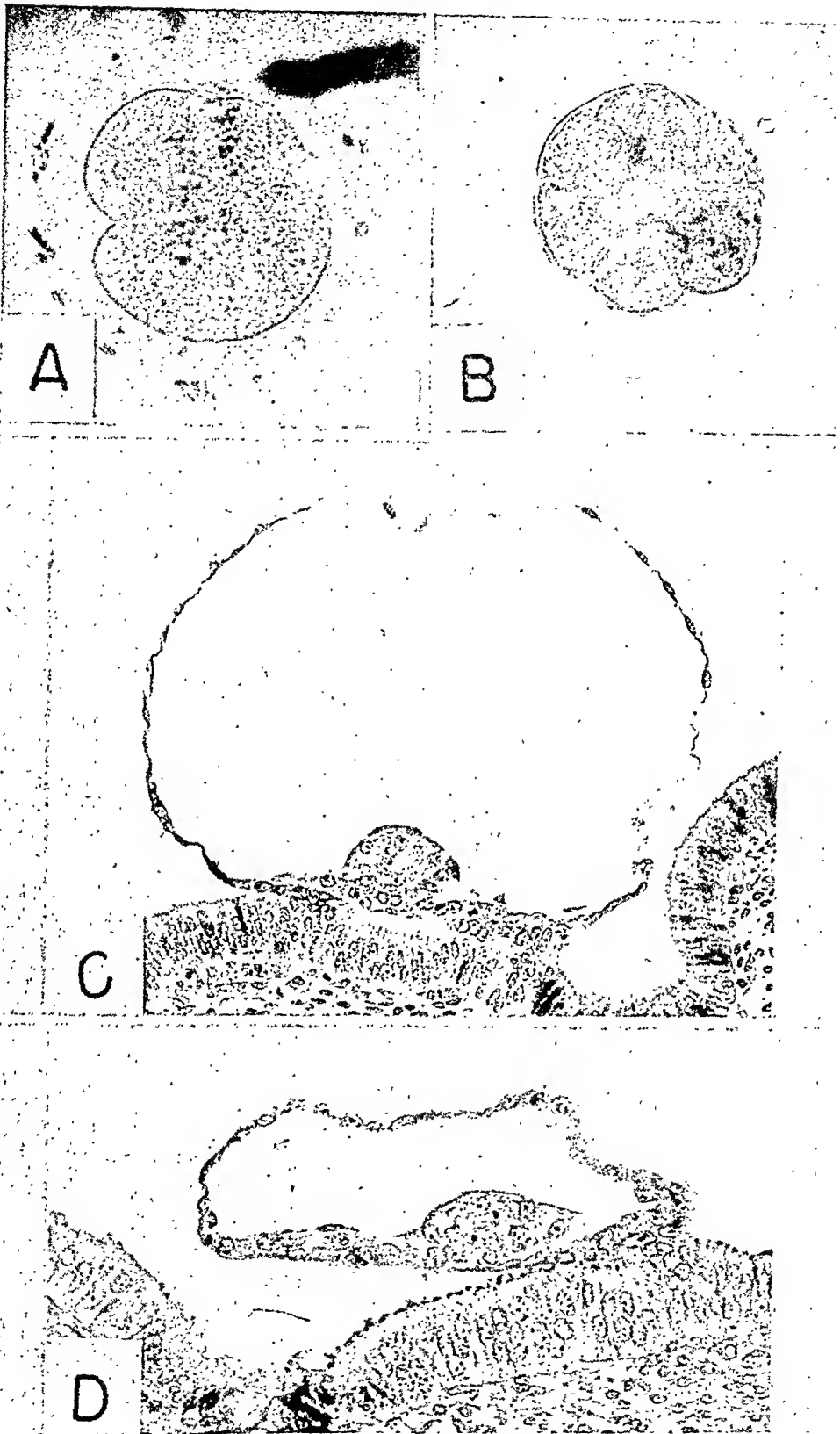


Fig. 1.—A. Two-cell human conceptus. Ovum fertilized in vitro. Two blastomeres, not quite of equal size, each containing single nucleus. One polar body. Several spermatozoa in the zona pellucida. (X300.)
B. Eight-cell human morula. Probably abnormal. Carnegie No. 8450. (X300.)
C. Blastocyst of rhesus monkey. In contact with endometrium. Carnegie No. 610. (X200.)
D. Nine-day blastocyst of rhesus monkey. Beginning its attachment to endometrium. (Figs. 1C and 1D are reproduced by courtesy and permission of Dr. Chester H. Heuser and Dr. George L. Streeter. In both figures the ventral surface of the inner cell mass is uppermost). Carnegie No. 520. (X300.)

Human development from the third to the seventh day is as yet obscure, but from Heuser's and Streeter's⁶ reports on several very early monkey ova we can imagine what must take place in the human being. Sometime between the third and sixth day, the multicellular morula acquires a central cavity to form the blastocyst (Fig. 1, C). Most of the hitherto contiguous cells spread out to form a cyst. Some of the cells remain grouped together at one pole of the blastocyst just within the enveloping layer. The newly formed spherical membrane will give rise to the trophoblastic or auxiliary structures: the smaller group of cells, to the embryo proper.

At nine days (Fig. 1, D) the multicellular monkey egg has differentiated into three major types of cells: those of the blastocyst wall which surrounds the fluid contained in the segmentation cavity; those much larger cells from which develops the embryonic disc; and the trophoblasts which are ready to eat their way into the endometrium. At nine days, the cystic monkey egg may still be free in the uterus, but about then, or soon after, it collapses and applies itself to the uterine wall. The human conceptus progresses more rapidly.

Thus, although already implanted, the youngest normally conceived human embryo we have seen is only about 7 days old (Fig. 2, A),* as judged by the time of coitus, the condition of the corpus luteum, and of the endometrium. Before fixation, it was not visible on the wall. After fixation, it was found to be about one-third of a millimeter in diameter. Stained sections showed that implantation was well advanced. We may say then that the human egg implants when about six days old and is comparable to the nine-day monkey blastocyst. How many of the first five days are spent in the tube, we do not know. As has been said, a specimen considered to be about three days old was found in the uterus. Perhaps the first day or two are spent in the tube where the morula is started. Probably during the fourth or fifth day the segmentation cavity is formed. Then occurs the differentiation into three kinds of cells, the primitive trophoblast of the blastocyst wall, the ectoderm of the embryo proper, and, beneath it, the endoderm. About the sixth day, the conceptus makes contact with the endometrium and the segmentation cavity collapses, as it does in the monkey. The newly differentiated syncytial trophoblast at the embryonic pole engrosses some of the superficial epithelium and as Streeter puts it, "forages" its way into this tissue.

After three days, as in our 9-day-old specimen (Fig. 2, B), the conceptus has become almost entirely surrounded by endometrium. It is now about one-half millimeter in diameter. The segmentation cavity has been redistended and within it is found the embryo proper. Two layers of this structure are well differentiated, and dipping into the ectoderm we see the enlarging amniotic cavity, which had been already visible two days earlier. This is bounded dorsally by the primitive amnion, the cells of which derive from the adjacent cytotrophoblast. The mass of syncytium has increased fully sixfold. Already spaces, lacunae, are formed within it. Separate at first, most, if not all, of these by the ninth day have communicated with each other to form a network of canals. Furthermore, the trophoblast has invaded the wall of at least one dilated sinusoid so that maternal blood, in small amounts, has flowed into the canals, thus bathing the syncytium. This is the origin of placental circulation.

Three days later, when the ovum is 12 days old (Fig. 2, C), progressive differentiation of the four tissues, already seen in their incipency, has built a sturdy, young organism. Over-all, it is about one millimeter in diameter, and is entirely within the endometrium, although the site of entry is not quite covered by closure of what will be the decidua capsularis. The embryo itself consists

*The stated ages of the embryo are made definite for "literary" reasons. Biologically these ages are only approximate.

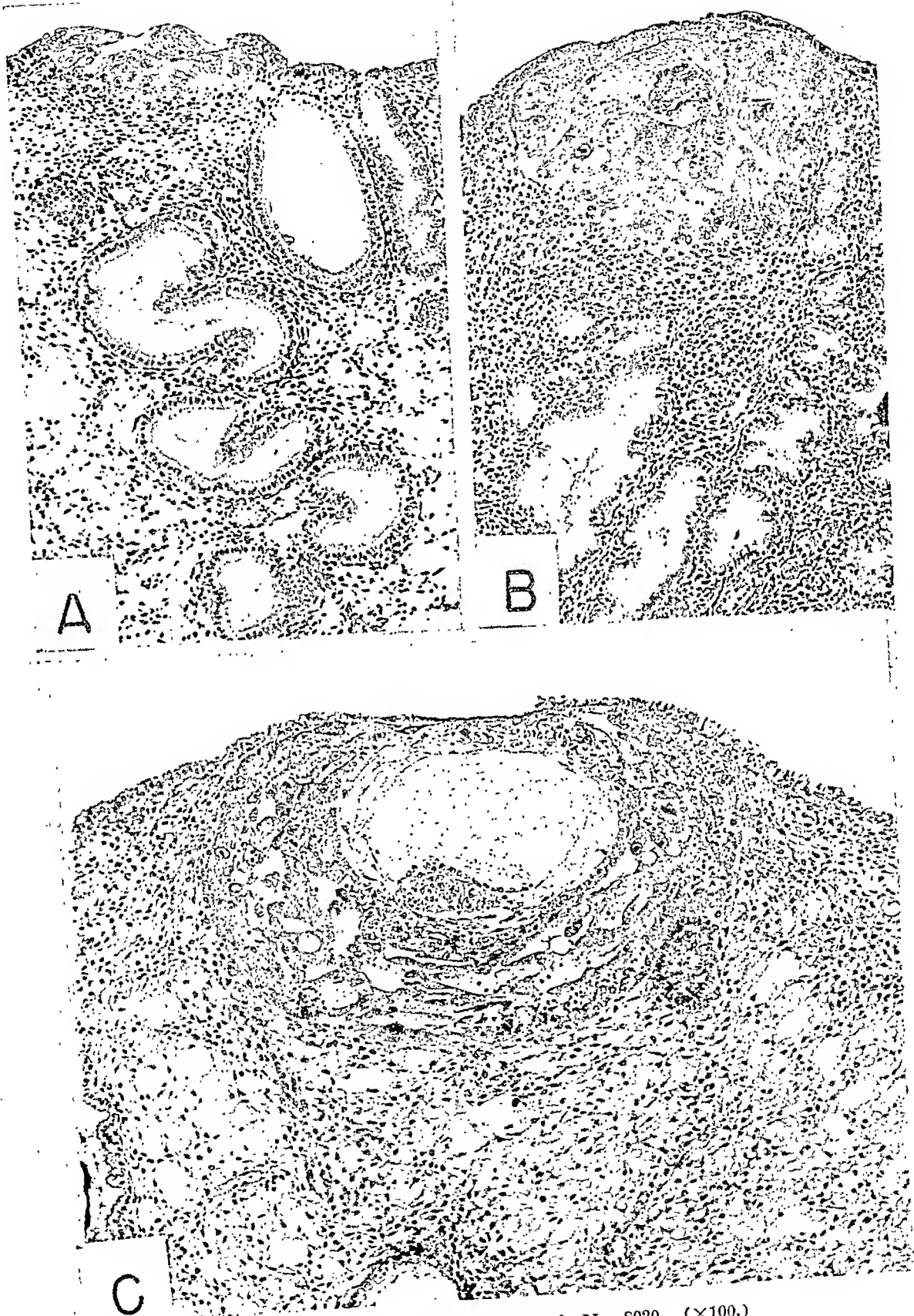


Fig. 2.—A. Seven-day human conceptus. Carnegie No. 8020. ($\times 100$.)
B. Nine-day human conceptus. Carnegie No. 8004. ($\times 100$.)
C. Twelve-day human conceptus. Carnegie No. 7950. ($\times 100$.)

of a pear-shaped plate about the size of a pinpoint, made up of a thicker pseudo-stratified ectoderm and a very thin ventrally situated endoderm. The cells of these two layers are delicately contiguous. They will later be separated by a third primary tissue of the embryo, the mesoderm. Dorsal to the ectoderm, bounded by it and the amnion, is the growing amniotic cavity that lies as a thin cyst on the back of the embryo. This still somewhat amorphous two-layer individual lies within a cavity fully five times its size. This is filled with fluid in which there is growing a diaphanous lacework of extraembryonic mesoblasts that divide this extraembryonic cavity, or coelom, into numerous chambers, one large and many small. The delicate net that joins the endoderm and with it surrounds the larger chamber is Heuser's membrane. We shall see that this is probably the *anlage* of the yolk sac. Surrounding this whole central space in which the embryo lies is the trophoblast, the all essential intermediary between the mother and the baby. This comprises two types of trophoblast derived from primitive tissue like that seen in the wall of the free monkey blastocyst: the cytotrophoblast that bounds the central cavity and the outer syncytium. The former gives rise to the mesoblastic network of the central cavity, and, on the outside, to the syncytium that is the commissary department of the whole organization. Since it made contact with the endometrium it has engrossed and digested the maternal stroma by which it grows, and dissolved a portion of a thin walled sinusoid, thus permitting increasing amounts of maternal blood to flow through the connecting lacunae formed within it. At this twelve-day stage, the syncytium constitutes about three-fourths and the cytotrophoblast the other one-fourth of the outer auxiliary portion of the conceptus.⁷

By the fourteenth day (Fig. 3, A), a significant change has occurred in the proportion and arrangement of the trophoblast that eventuates in a more efficient utilization of maternal blood. The inner cytotrophoblast grows rapidly. It started as not much more than a single-cell layer, but by the fourteenth day it is arranged in masses of single cells that project outward into the syncytium. Except in the outermost portion connecting with the endometrial stroma, this syncytium now forms only a thin layer of cytoplasm lining the lacunae. The proportions have changed: the greater part of the trophoblast is made of individual cells; there is proportionately less of the foraging syncytium.⁷ Once maternal blood is available it is apparently no longer necessary to consume much solid tissue.

Equally striking and significant are the papillary projections of the primitive mesoblast into the focal areas of the cytotrophoblast. This forms a thin wall over the projections, some of which are seen to extend into the lacunae. Within these evaginations, the primitive mesoblast builds a network in which will form the terminal placental blood vessels of the fetus. Thus do the villi arise.

Meanwhile, the mesothelial sac lying just ventral to the endoderm has become markedly smaller by a process not completely understood. It has become the yolk sac, an important structure for the further development of the embryonic end of the fetal vascular system. The amnion, too, is assuming its enveloping functions for we see its membrane has grown around the border of the ectodermal disc to make juncture with the mesothelial covering of the yolk sac. Most of the baby is now on its way into the amniotic cavity where we find it at term.

All this has occurred in about fourteen days. At the time of the first missed menstrual period, we have the ground plan of the placenta, a yolk sac, a completed amniotic cavity, and an embryo comprising undifferentiated ectoderm and a thin layer of endoderm. The whole conceptus is only about three millimeters in diameter, and is essentially engrossed within the endometrium. Sur-

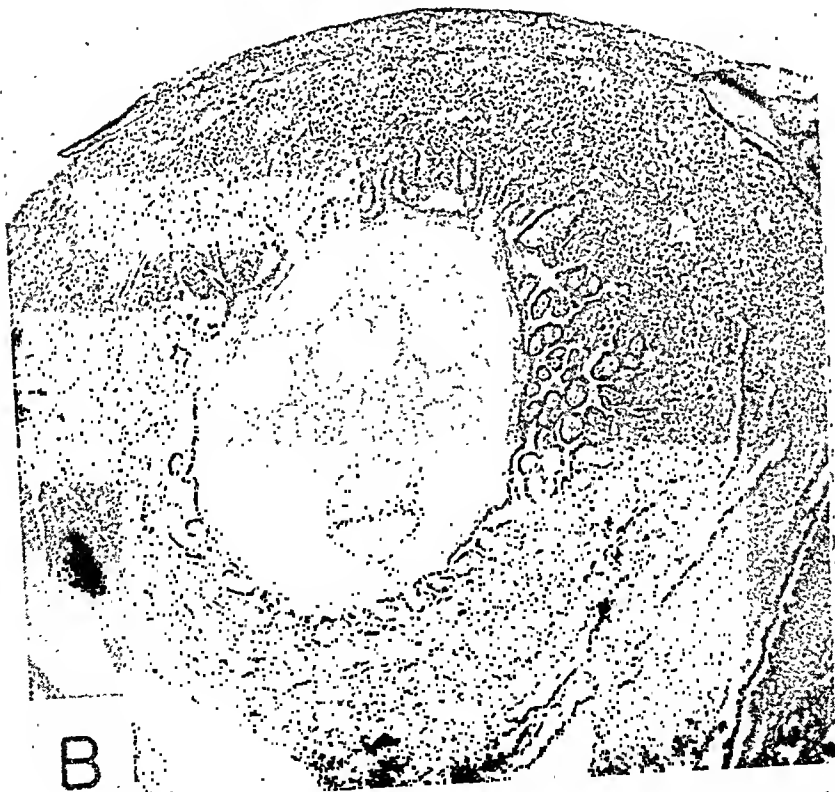
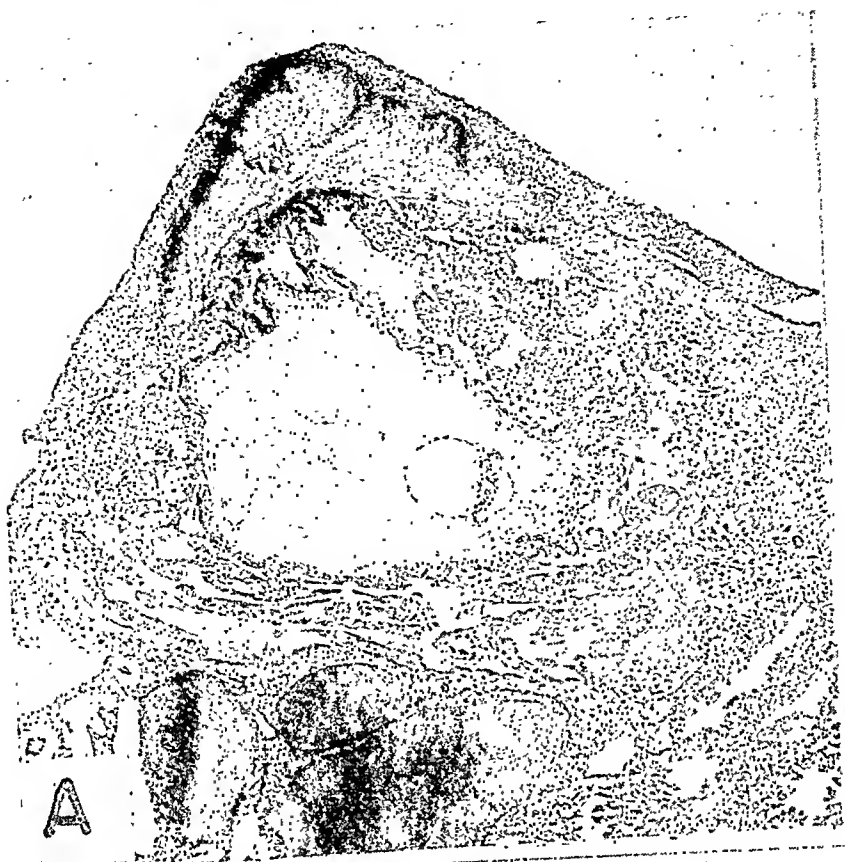


Fig. 3.—A. Fourteen-day human conceptus. Ventral surface of embryonic disc is to the left. Carnegie No. 7801. (X35.)
B. Sixteen-day human conceptus. Ventral surface of embryonic disc is uppermost. Carnegie No. 7802. (X30.)

rounding it are dilated maternal arteriovenous sinusoids that indirectly, by way of the intervillous space, communicate with the lumina of several glands into which blood has flowed in such a way that it can, and doubtless does, flow into and then out of the uterine cavity. Over one fourteen-day specimen (Fig. 3, A) is a mound of coagulated blood that has leaked through a tiny break in the trophoblast at the abembryonic pole. Toward the end of the sixteenth day (Fig. 3, B), we see what begin to look like mature placental villi surrounding the entire extraembryonic cavity. In serial sections, these are shown to be branches of the mesoblastic buds derived from the primitive extraembryonic mesoblast and surrounded by both kinds of trophoblastic tissue. At this time, the embryo, too, is entering the stage of previously known embryology. Heuser has reported the primitive streak as being in formation on the ventral surface of the ectoderm.⁷

As of June, 1947, our series of very young embryos, excluding those fertilized in vitro, amounts to twenty-six. Of the total, twelve are considered abnormal—47 per cent.

Three of them are in the stage of undifferentiating cleavage. Two of these are surely abnormal and the other is as yet considered so. Two of the implanted specimens consist only of trophoblastic tissue, having no embryo proper. Of the other imbedded ova, four have apparently normal embryonic discs but defective accessory structures; one has apparently adequate placenta-making material but a defective embryo; and in two, both parts of the conceptus are abnormal. Thus they all might and some surely would have aborted. Does this mean that 47 per cent of conceptions in normal fertile couples are doomed even before the first period has been missed? In some of these cases, the conceptus is so abnormal that probably no period would have been missed at all; the pregnancy would not even have been known to exist. These specimens are too few to give a conclusive indication of abortion frequency. They surely do not suggest that 47 per cent of recognized pregnancies may be aborted.

Our material has been collected by Hertig from uteri removed for various therapeutic reasons from women who had demonstrated normal fecundity, and who with one exception kept a record of the coital dates just preceding their operations. In each case there was a recent corpus luteum. To get these twenty-six specimens, one hundred twenty-two organs have been carefully searched. This might suggest a pregnancy rate of 21 per cent, but by correlating the dates of coitus with the ovulation period as determined by the endometrium, it was found that eighteen patients were probably not exposed during the ovulation phase. Among the cases in which coitus did occur during this time, 25 per cent were found pregnant. Unless some ova were missed, which is doubtful, we are led to believe that during any given cycle, a potentially fertile couple has not more than a 25 per cent chance of establishing a pregnancy that might persist long enough to suppress menstruation. It will be remembered that three of the specimens were found free in the uterine cavity and at least two are abnormal. Their prospect of normal implantation is unpredictable.

These twenty-six fertilized ova with associated maternal tissue give strong indication as to the time of ovulation in the menstrual cycle. The age of each conceptus as estimated by Streeter and Hensen, together with the immediately

preceding menstrual habit of the patient, the age of the endometrium,⁸ and of the corpus luteum,⁹ all tend to prove that in long or short cycles, ovulation occurs about the fourteenth day before the onset of menstruation.¹⁰

Summary and Conclusions

1. Human ova obtained from unruptured follicles can be fertilized in the laboratory and cultured to the three-cell stage. All such eggs, though normal in appearance, are not equally susceptible to fertilization.

2. In nature, human eggs are probably fertilizable for not more than twelve hours. Spermatozoa are apparently capable of fertilizing the egg for at least forty-eight hours after ejaculation. The human egg reaches the eight cell stage in three days after ovulation.

3. The fertilized human egg may have reached the uterus as early as the third day after ovulation. On about the sixth day, as a blastocyst, comprising three differentiated tissues, primitive trophoblast, ectoderm and endoderm, it makes contact with and begins ingestion of the maternal endometrium.

4. When nine days old, i.e., during the tenth day of development (on about the twenty-fourth day of a twenty-eight day cycle), the ovum has become interstitial in the endometrium, and has an average diameter of about one-half millimeter. The embryonic disc, comprising ectoderm and endoderm is well defined. The amnion is in formation. The larger part of the trophoblast consists of syncytium in which has appeared many communicating lacunae. Entrance has already been made by the syncytium into a maternal sinusoid, thus permitting maternal blood to flood the lacunar system.

5. When twelve days old, the conceptus is almost one millimeter in diameter; the embryo itself is about one-tenth as wide, and lies in a cavity about five times bigger than itself. This extraembryonic coelom is lined by a network of a fifth tissue, derived from the cytotrophoblast, the extraembryonic mesoblast, or mesoderm (not to be confused with the actual mesoderm of the embryo which appears later).

6. By the fourteenth day, the amniotic sac has covered the ectoderm. The mesoblast has formed many extensions from the cavity into the cytotrophoblastic mass, and has stretched the proportionately diminishing syncytiotrophoblast into a thin covering layer that then lines the lacunae. In these papillary outgrowths, the extraembryonic mesoderm extends to form a supporting structure. Maternal blood fills the lacunar spaces. Endodermal cells have proliferated to form the definitive yolk sac. The conceptus after fixation is from two to three millimeters in diameter.

7. By the sixteenth day, branched villi of mature appearance, but without a completed vascular structure, are formed. The primitive streak appears on the ventral surface of the ectoderm.

8. Forty-seven per cent of twenty-six embryos are abnormal in either trophoblastic or dermal tissue or in both. Two of the imbedded specimens lack the embryonic disc or inner cell mass.

9. In one hundred twenty-two uteri of proved fertile women, one hundred four of whom had ovulated and been exposed to pregnancy during the ovulation phase, only twenty-six conceptuses were found. Assuming none was missed, this gives a fertility index of only 25 per cent.

10. Ovulation in twenty-six well authenticated cases occurred about the fourteenth day before the expected onset of menstruation.

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Discussion

DR. CARL HUBER, Indianapolis, Ind.—It seems to me that nothing can be more remarkable than this presentation. When one realizes the tremendous advances that have been made in human embryology in the past few years, the greatest credit must be given to Dr. Rock, his co-workers in Boston and at the Carnegie Institute.

As our knowledge increases, it becomes apparent how greatly the information obtained from the monkey has added to our knowledge of human reproduction. But it also has shown how important accurate study of these early stages in the human being itself has become. The variation of implantation from the sixth day in the human to the ninth day in the monkey is an example of these differences. This may perhaps be explained on the basis of the superficial implantation in the monkey and the interstitial type of implantation in the human. As our knowledge of these early stages increases, the time interval during which conception may occur seems to become shorter and more definite. If ovulation takes place with little variation fourteen days before menstruation and the ovum survives for only twelve hours, it is not surprising that only 25 per cent of apparently correctly timed exposures result in fertilization of the egg.

It is interesting that in an earlier report concerning twelve early embryos, 42 per cent were abnormal, and that in the present larger series 47 per cent showed abnormality. At that time it was suggested that this rate of abnormality, 42 per cent, was much higher than anticipated, and now that the series increases, the frequency of early abnormal embryos becomes still greater. It would be interesting to learn if as many of the abnormal ova were implanted on the anterior wall of the uterus as reported in the previous communication some years ago.

It is also very interesting to note the lack of hemorrhage associated with implantation until approximately the time of the next expected menstrual period. It is clear from the pictures that there was practically no hemorrhage until from the twelfth to the fourteenth day, and then considerable hemorrhage surrounded the ovum and broke through into the endometrial areas. As previously suggested, then, the appearance of blood at the time of the expected menstrual period may be a sign of implantation and the source of confusion concerning the time of onset of the pregnancy.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—In keeping with what we have learned to expect from Dr. Rock, this is a valuable and welcome contribution, since it recapitulates and integrates, particularly from the viewpoint of embryologic timing, the series of monographs issued during the past ten years under the authorship of Rock and his associates. This group of papers has opened up new horizons in embryology; and to say that it constitutes one of the major contributions to embryology and obstetrics of our time would be merely to reaffirm a fact recognized wherever embryology is known. These alterations which Dr. Rock has described so graphically in the early fertilized ovum as they occur from day to day may be regarded as the workings of the genes. They are the long-continued progressive effects of gene action. They are primarily genetic in character.

Because of the magnitude of the task of unravelling all of these morphologic changes which have been described, Dr. Rock and his associates have focused their attention on these phenomena and have chosen to say very little about a certain factor which may drastically affect this series of specimens. I refer to the role of environment in the development of the early ova, a problem which is of far-reaching clinical importance. Environment may produce decided changes in the development of the early ovum. For instance, in primitive forms of life, it is well known that changes in the cell concentration of the fluid surrounding the developing ova may work havoc with normal development. The same is true in many experimental animals when their diet is deficient in certain food essentials.

One of the most interesting ways in which environment may produce changes of ovular development is to be found in tubal twinning. We know that when twins are encountered in the uterus the ratio of monozygotic twins to dichorial twins is one to three; but, as Arcy showed some years ago, when twins are implanted in the tube, this ratio is no longer one to three, but fifteen to three. In other words, there is something about the environment which the ovum encounters when it implants in the tube which brings about abnormality at an early stage and results in twin embryos.

Another role environment plays in causing deviations from the normal in ovular development is in diabetes. It is common knowledge that congenital anomalies in infants of diabetic women are not infrequent. In a few months Dr. Priscilla White will report a large series of children of diabetic mothers, in which she will cite a high incidence of developmental anomalies. Some of these defects may be minor, it is true, but the figure which she will report is about 25 per cent.

The Australian experience with rubella is another example of how environment may affect embryologic development. Dr. Rock reports an incidence of 47 per cent of abnormal ova; and the question arises whether some of these may not have been due to the pathologic changes which prompted the hysterectomy. He pointed out that these hysterectomies were done advisedly, and I am wondering whether these alterations, through producing unfavorable environment, may not have played a role in his very high incidence of defective ova.

The importance of environment, then, in the development of the early ovum is well established; moreover, it has a very definite clinical bearing because the most common cause of abortion is a defective conceptus. But the question is: why is the conceptus defective? Is it the result of original faulty genes or the result of faulty environment? The embryologic work of Mall as well as Streeter shows that most abortions are due to faulty ova, and the latter, in their opinion, are usually due in turn to faulty genes. If this is true we are wasting our time in treating threatened and habitual abortion because this accident is foreordained. On the other hand, there is accumulating evidence to indicate that faulty genes are probably not as common as some have believed, and that faulty environment plays a larger role in abortion than was formerly thought. If poor environment does loom large in this picture, then we are fully justified in trying to correct it and in searching more intently than in the past to discover its causes. I hope Dr. Rock in his closing remarks will state whether he has been able to correlate to any degree whatsoever these abnormal ova with abnormal environmental conditions, and give us his general opinion in regard to the respective roles of the genes and environment in causing abortion.

DR. KARL M. WILSON, Rochester, N. Y.—I would like to ask Dr. Rock to describe the technique used in recovering the ova. More of this material could be obtained if more of us become interested in attempting to recover it and then arrange to send the material to Dr. Rock's laboratory or some other embryologic laboratory for study.

In discussing the development of the core of the chorionic villus, I wonder if he has observed anything in the way of delamination of the trophoblast as a source of origin for this tissue. Streeter feels that this is the important origin if not the only source of origin of the mesodermal tissue in the chorionic villi, that is to say a delamination of trophoblast and then its differentiation into mesoderm. In a seventeen-day specimen I described several years ago, it seemed to me that this could be demonstrated reasonably satisfactorily.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—I understood Dr. Rock to say that the mesoderm is driven from the trophoblast into this tissue and that this cystotrophoblastic layer produces a syncytiotrophoblast. What is the relationship of this phenomena to the disappearance of the Langerhan's layer?

In the limited work I have done myself in this field, it has seemed to me that I have many times seen the pinching off of Langerhan's layer into the mesoderm core of the cells. The mesoderm often resembles the similar elements of Langerhan's layer. We know that the Langerhan's layer eventually disappears and it may be that it is due to the eventual disintegration of the layers. Certainly the microscopic appearance of tissues would suggest it does take place and it may be that the so-called protective cells of the placenta and the chorionic mesoderm are derived from the same order.

DR. EMIL NOVAK, Baltimore, Md.—When one stops to think that up to twenty-five years ago no one had ever seen a human egg except as it exists in immature form in the ovary or when, after fertilization, it has already implanted itself in the endometrium, the importance of these contributions of Rock and Hertig can be all the more fully appreciated. For many years the Miller ovum remained the real aristocrat among the young eggs which had been discovered, but in this egg, estimated to be about ten and one-half days old, the amnion had already been formed, and we could only speculate about its derivation, as well as about other early features, which have been largely clarified by the study of the much earlier stages which Rock and Hertig have made available.

One point which interested me greatly in these slides was the variation in the degree of decidual response in eggs which are presumably of about the same stage of development. The Miller egg, of which I was fortunate enough to see the original sections, showed almost no decidual change in the stroma cells, and yet one of the specimens we have seen today is of almost exactly the same age, and it shows a rather full blown transformation of the stromal cells into large, polyhedral and typically decidual cells. I wonder if Dr. Rock has been impressed with this variability in the degree of decidual reaction?

Dr. Eastman spoke of this work as representing a major contribution to embryology. Although I am not an embryologist, it seems to me to represent the most important contribution of our generation in this field.

DR. ROCK (Closing).—In answer to Dr. Novak's question about the endometrium: It is surprising how variable this can be in the different ages of eggs. Some of the endometrium is in the edematous phase, showing that the conceptus must have got into a tissue that had not gone that far, or else the edema had lasted longer than was to be otherwise expected.

Dr. Huber has called attention to the decidualike reaction around the embryo. It seems to be a very localized effect.

Dr. Wilson will forgive me for not taking time to describe my method of selecting cases and Dr. Hertig's fairly simple but meticulous technique of examination, for the details have been published in *Contributions to Embryology*, number 184, page 121, Carnegie Institution of Washington Publication.

Regarding Dr. Montgomery's remarks: I expected the discovery that I am not an embryologist. I do not know where the mesoblasts come from. The extraembryonic meso-

blasts which have formed the network in the segmentation cavity come from the cytotrophoblast, and this network extends outward in the evaginations of the cytotrophoblast that will develop into villi.

The only pathology in the endometrium found in our cases was that associated with one of the abnormal eggs that had no embryo. This implantation site was polypoid. In the rest of them we could find no abnormality of the endometrium as far as the cytology of this tissue and its staining quality are concerned. There is much to be learned about maternal environment, for, as Dr. Eastman has brought out, this must have a great deal to do with growth of the ovum, especially in these early stages. It seemed at one time that eggs probably do not take much from their tubal environment. They needed warmth and moisture and transportation. Now we know the very young ova increase slightly in size, so they must acquire something. Of course, the zona disappears, but just how they carry on before they implant we do not know.

The question arose as to the site of implantation. Of the twenty-three implanted specimens, fourteen were normal. Of these, five were on the anterior wall, and nine on the posterior wall. Nine were abnormal. Of these, six were on the anterior, and three on the posterior wall.

Time forbids adequate discussion of the possible likely causes of abnormal development during the first ten days after fertilization. The determinants of cellular differentiation and orientation are obscure. I would suppose that the intrinsic protoplasmic quality of the ovum as affected by intrafollicular conditions and by age, as well as the modification of the directive genes of both egg and spermatozoön might affect the orderly cleavage and arrangement of blastomere quite as much as would environmental factors.

STUDIES OF THE HUMAN CORPUS LUTEUM*†

Corpus Luteum-Endometrial Relationships in Functional Uterine Bleeding*

JOHN I. BREWER, M.D., PH.D., AND HAROLD O. JONES, M.D., CHICAGO, ILL.

(From the Department of Gynecology and the Henry Baird Favill Laboratory of St. Luke's Hospital, and the Department of Gynecology of Northwestern University Medical School)

THE purpose of this paper is to present a histologic study of corpora lutea and endometriums in instances of functional uterine bleeding, and to discuss the relationships of these two tissues.

The term "functional uterine bleeding" is used here in the same manner as defined by Curtis.¹ He stated that this type of bleeding includes endocrinopathic cases with bleeding and also bleeding cases which may not be attributable to endocrine disorders. The material presented here may throw some light on the latter type of bleeding. Most authors include under the designation of "functional uterine bleeding" only those cases in which there is no associated gross pelvic pathology. It is our belief that "functional uterine bleeding" can occur and that the ovarian and endometrial tissue changes are identical irrespective of the presence or absence of gross pelvic pathology. It is, therefore, not logical to exclude instances of such bleeding in the presence of gross pathology from the classification of "functional uterine bleeding" merely because of the presence of the pathology.

Material

The specimens in each instance were obtained by hysterectomy and oöphorectomy or by resection of the corpus luteum. The operations were performed during the bleeding phase, since it is during this period that most accurate interpretations can be made. Tissues obtained during a nonbleeding period cannot be accurately evaluated because one cannot foretell the date of onset of future bleeding, its duration, or its character, and because it is frequent for a normal cycle to be interposed amongst abnormal cycles.

SPECIMEN No. 335.—Aged 40 years; para iv, gravida iv; operated on day 27

Menstrual history: Onset at 12 years; thirty-day cycles with three days flow until four months prior to operation. The last four cycles ranged from twenty-one to twenty-seven days in length with eight days flow.

Operation: Complete hysterectomy and bilateral salpingo-oöphorectomy.

Pathologic diagnosis: Multiple uterine fibroids and bilateral chronic salpingitis.

Corpus luteum: The corpus luteum was 1.1 by 1.0 by 0.6 cm. after fixation. The wall was in the usual folds. The granulosa lutein cells were not large, and histologically appeared to be intact functioning cells (Fig. 1). Only an occasional cell evidenced regression. The cells stained evenly and had large round

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or oval nuclei. Some nuclei were huge. Throughout the granulosa lutein layer there were many dilated blood-filled vascular channels. The connective tissue in the border about the central cavity was meager in amount, and was not arranged in an organized layer (Fig. 1). In some regions along the inner edge of the granulosa lutein layer small groups of partially degenerated nonluteinized granulosa cells extended into the cavity. This was observed frequently in young corpora lutea.



Fig. 1.—Specimen No. 335. The corpus luteum has persisted in the vascular stage with little evidence of regression until day 27 of the cycle and menstruation is beginning (see Figs. 2 and 3).

Endometrium: The endometrium was as thick as 0.2 cm. after fixation. There was a superficial infiltration of lymphocytes and leucocytes. The stroma was dense. The glands were squashed. The glands and gland cells were typical of a secretory pseudopregnant endometrium (Fig. 2). In one small region the surface epithelium was wanting, and the epithelial cells immediately adjacent were degenerated (Fig. 3). From this region there was evidence of bleeding into the uterine cavity with slight desquamation of tissue.

Interpretation: The corpus luteum had persisted in the vascular stage without evidence of degeneration for a prolonged time.

The glands of the endometrium were more fully stimulated than is usual with a corpus luteum in the vascular stage. Prolonged action of a functioning corpus luteum in the vascular stage might account for this excessive stimulation.

Involution, infiltration of leucocytes and lymphocytes, and localized bleeding indicated impending menstruation.

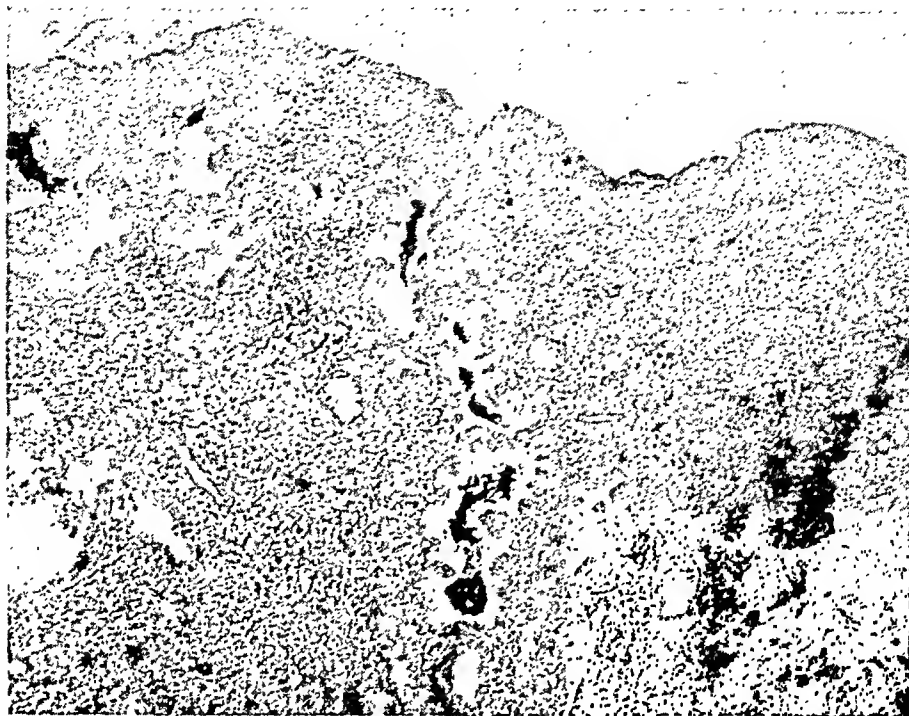


Fig. 2.—Specimen No. 335. The pseudopregnant type endometrium has involuted.

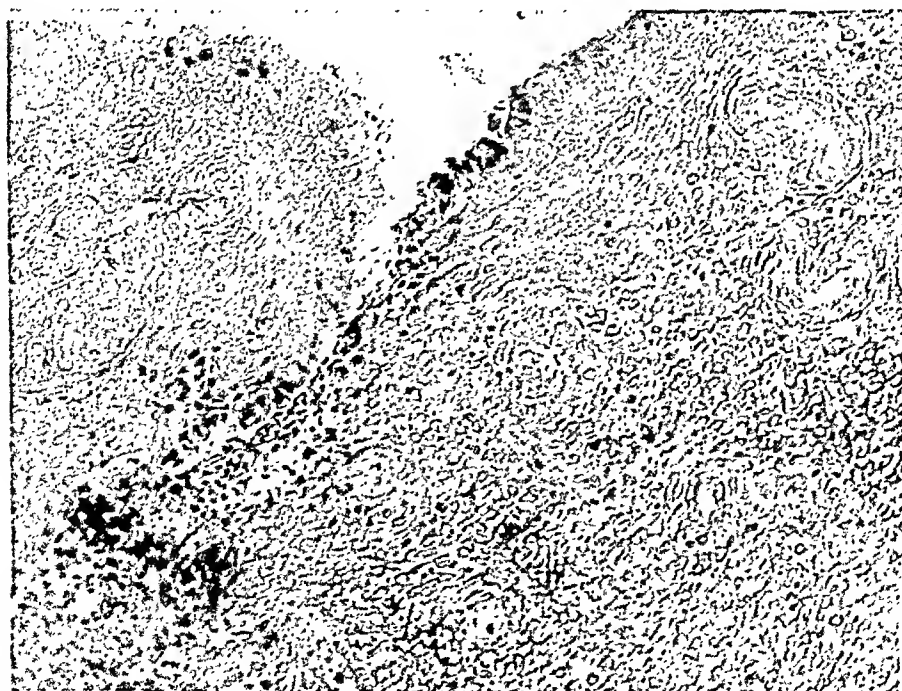
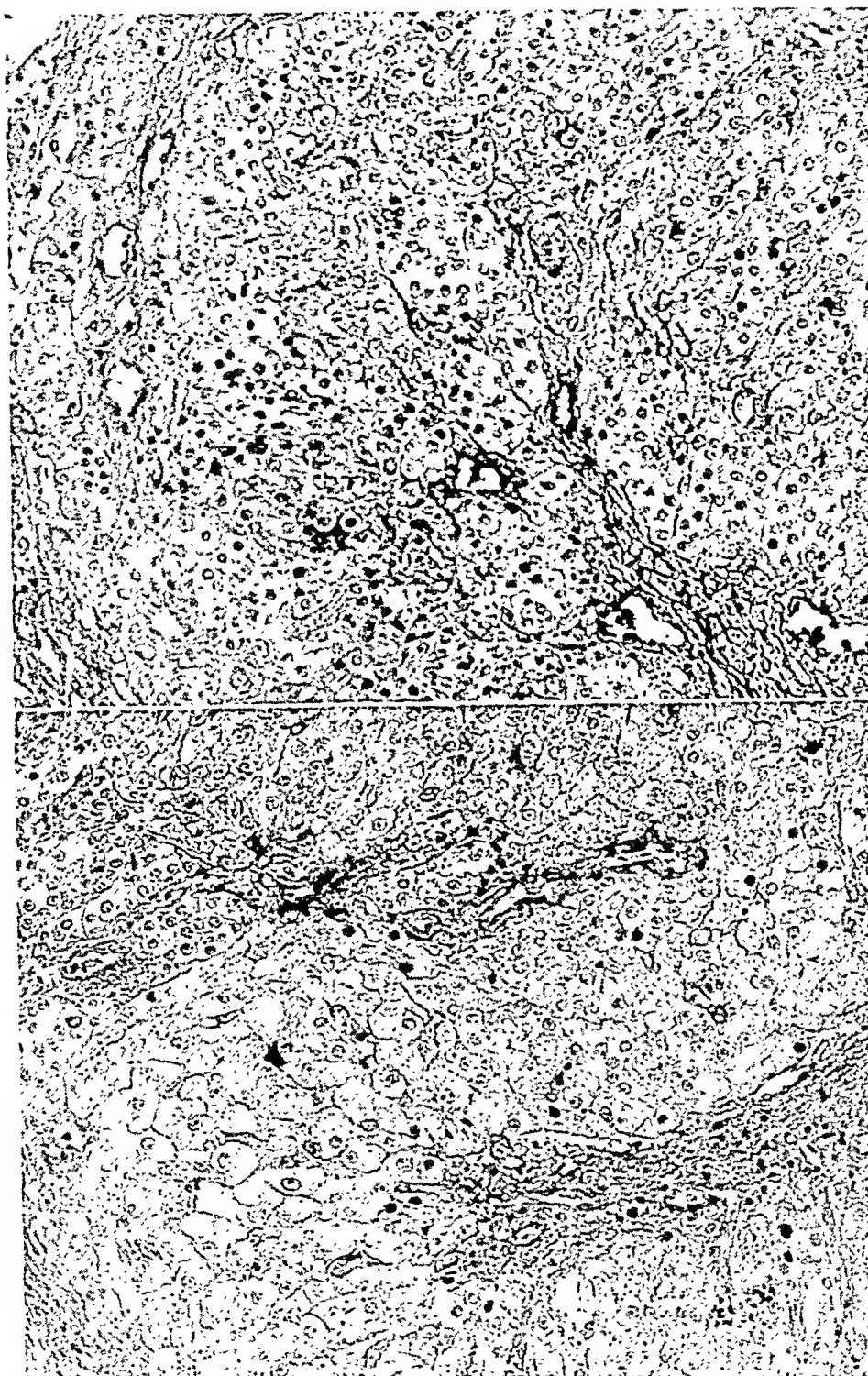


Fig. 3.—Specimen No. 335. In a small region desquamation of the surface epithelium of the endometrium has occurred and bleeding from this region is evident.



• Fig. 4.—Specimen No. 332. Many of the granulosa lutein cells evidence degeneration. In other portions of the corpus luteum the cells evidence considerably less degeneration (see Fig. 5).

• Fig. 5.—Specimen No. 332. On day 14 of continuous bleeding the granulosa lutein cells in this portion of the corpus luteum retain histologic evidence of functional activity. Some of the endometrial glands reflect this activity (Fig. 7).

The corpus luteum, however, had not undergone the degree of degeneration that is usually present at the onset of bleeding. In the life cycle of a normal corpus luteum some time is required to bring about complete regression of the gland after termination of the vascularization stage. In this specimen the vascular stage had persisted, and it was believed that complete regression would have required several more days. Since menstruation was impending, it was most probable that corpus luteum function would continue after the onset of bleeding, and that the period of flow would be prolonged as a direct result of prolonged activity of the corpus luteum.

This specimen represents an early phase of prolonged activity and life of the corpus luteum and irregular shedding of the endometrium.

SPECIMEN No. 332.—Aged 36 years; para 0, gravida 0; operated on day 14 of continuous bleeding.

Menstrual history: Onset at 14 years; twenty-eight to thirty day cycles, with four to five days flow until six months prior to operation. During these six months bleeding occurred every fourteen to twenty-one days. The last period of bleeding began fourteen days before operation, and bleeding was still present at the time of operation.

Operation: Hysterectomy and right salpingo-oöphorectomy.

Pathologic diagnosis: A single one centimeter intramural fibroid.

Corpus luteum: Prior to fixation the corpus luteum was 1.8 by 1.2 by 1.0 cm. It had a pale yellow wall and a gray-red centrum. Most of the granulosa lutein cells were shrunken, vacuolated, irregular, and had small nuclei (Fig. 4). In a few regions the granulosa lutein cells were large, had evenly stained finely granular cytoplasm, large round or oval vesicular nuclei, and appeared similar to functioning cells (Fig. 5). The central cavity had a dense well-organized connective tissue border. There was a moderate amount of connective tissue throughout the granulosa lutein layer. The theca cells were small, vacuolated, with small well-stained nuclei.

Endometrium: The endometrium prior to fixation was as thick as 0.2 cm. The surface was irregular and had no surface epithelial covering. At one place resting upon the surface was a mass of red blood cells with small intermingled degenerating endometrial gland and stromal tissues (Fig. 6). The endometrial desquamation in some regions reached down to and into the basal zone. Some of the glands had cells with peripheral secretory vacuoles (Fig. 7), and others showed evidence of antecedent secretory activity. Others were straight with narrow tall columnar cells and without evidence of secretory activity (Fig. 6). Only an occasional epithelial cell in mitosis was found, indicating that there was little active tissue growth. The stroma was dense and contained only a small amount of blood. No stromal cells in mitosis were found.

Interpretation: The degenerated granulosa lutein cells were no more degenerated than those seen at times in day 1 to 5 specimens.

Some groups of granulosa lutein cells showed little degeneration and appeared histologically similar to functioning granulosa lutein cells. Such cells in specimens fourteen days after onset of menstruation were not normally found.

The size of the corpus luteum was large for a day 14 specimen of the previous cycle.

The endometrium had not healed. There was no evidence of any active tissue growth.

Some glands retained secretory evidence and some did not.

This specimen represents an instance of prolonged activity of the corpus luteum and prolonged and irregular regression of the endometrium fourteen days after the onset of bleeding.

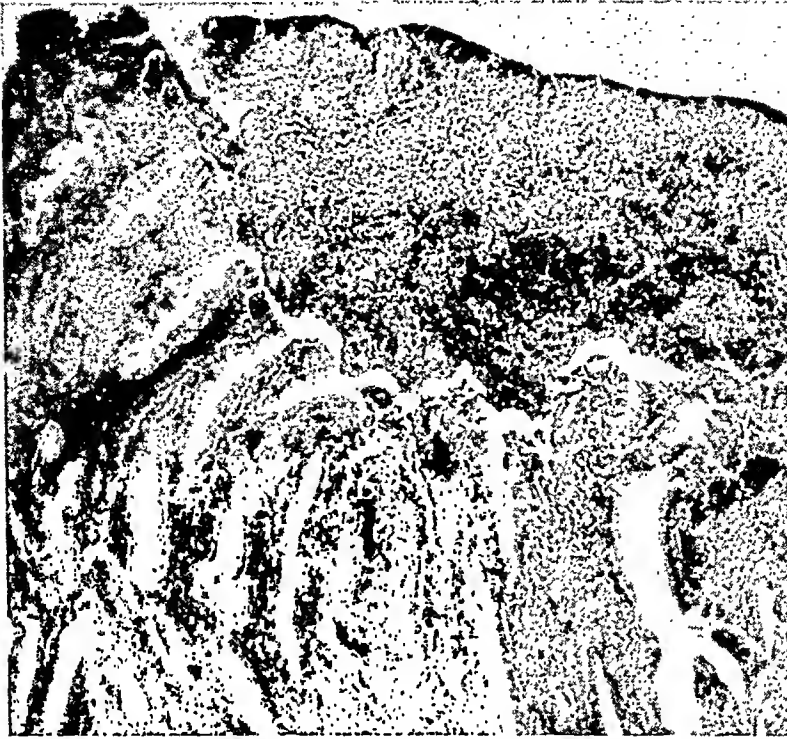


Fig. 6.—Specimen No. 332. The endometrium desquamation has occurred. Masses of cellular debris and blood cells rest upon the surface. Healing of the endometrium is lacking. Some of the glands are narrow, straight, and without secretory activity.



Fig. 7.—Specimen No. 332. The endometrial glands in some regions are secretory in character indicating continued and prolonged corpus luteum activity (see Fig. 5). Figs. 6 and 7 portray tissue changes typical of irregular shedding.

SPECIMEN No. 334.—Aged 40 years; para 0, gravida 0; operated on day 8 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight day cycles, with eight days profuse flow for the ten years prior to operation. The last menstrual period began April 8, 1940, and the patient was still bleeding at operation on April 15, 1940.

Operation: Complete abdominal hysterectomy and bilateral salpingo-oophorectomy.

Pathologic diagnosis: A single 1 cm. intramural myoma, bilateral hydrosalpinx, and endometriosis.

Corpus luteum: The corpus luteum before fixation was 1.5 cm. in diameter with a wavy yellow wall. The central cavity contained a straw-colored fluid. Around the inner edge there was a layer of hemorrhage. Microscopically the wall of the corpus luteum was arranged in the usual folds. The granulosa lutein cells were for the most part large. Vacuolization of the cells was quite marked. Some cells had pyknotic nuclei, most, however, had intact round or oval vesicular nuclei. There was a marked vascularization of the entire layer. The connective tissue had grown through the granulosa lutein layer, but the amount projecting into the central cavity was meager and was not organized. There were frequent blood sinuses along the border of the central cavity. Along the inner edge in some regions were masses of small granulosa cells with vacuolated cytoplasm and pyknotic nuclei.

Endometrium: The endometrium was as thick as 0.2 cm. after fixation and staining. In most regions the surface epithelium was lacking. The glands project above the irregular endometrial surface. In most places the glands showed no evidence of secretory activity, were straight, and were lined by tall thin columnar cells with flattened nuclei. There were some glands that had centrally placed nuclei and had basal vacuoles. Epithelial cells in mitoses were extremely rare. The stroma was everywhere dense. Those portions of endometrium with intact surface epithelium were typical of a postmenstrual type.

Interpretation: On the eighth day of menstruation the corpus luteum was large, vascular, and had little evidence of regression.

Some portions of the endometrium had regressed, desquamated, and healed, while others were still in the process of desquamation. Those glands that had some secretory activity were of the early secretory type.

The findings were indicative of prolonged life of the corpus luteum with irregular and prolonged regression of the endometrium.

SPECIMEN No. 293.—Aged 44 years; para ii; gravida ii; operated on day 45 of bleeding.

Menstrual history: Onset at 12 years of age; twenty-seven to twenty-eight day cycles with four to five days flow. During the two and one-half years prior to operation the flow became profuse and prolonged, lasting as long as fifteen days. The last period of bleeding began Oct. 8, 1939, and had continued daily up to and including the day of operation, Nov. 21, 1939.

Operation: Hysterectomy and bilateral salpingo-oophorectomy.

Pathologic diagnosis: Uterine myomas and chronic fibrous salpingitis.

Corpus luteum: The corpus luteum before fixation measured 0.8 by 0.5 by 0.4 cm., and had a thick, wavy, yellow wall. The corpus luteum was histologically typical of a postvascular stage (Fig. 8). The majority of the cells were small, regular in outline, stained evenly, and had well-stained round or oval vesicular nuclei. Some cells in various regions of the layer were highly vacuolated, shrunken, irregular, and had pyknotic nuclei. The blood vessels throughout the layer were straight, thick walled, narrow, and, except in rare instances,



Fig. 8.—Specimen No. 293. On day 45 of continuous uterine bleeding the persistent corpus luteum is typical of the postvascular stage. Its secretory activity is indicated by the endometrial reaction (see Fig. 9).

Fig. 9.—Specimen No. 293. In this portion of the endometrium the glands evidence secretory activity. The intercellular fluid forms lakes. Adjacent (arrow) endometrium is partly sloughed and is bleeding (compare with Fig. 10).

contained no blood. The ingrowth of connective tissue was moderate, and that which extended into the central cavity was organized into a moderately thick border.

Endometrium: The endometrium after fixation and staining was as thick as 0.2 cm. The histologic appearance varied greatly in different portions of the uterus. In some regions the tortuous glands evidenced secretory activity (Fig. 9). These regions had intact surface epithelium. The large amount of intercellular fluid in the endometrium formed lakes in some places. The stromal cells were widely dispersed by this fluid. While this portion of the endometrium was secretory in character, it did not have the exact characteristics of a normal secretory endometrium. Adjacent to the above described region was a depressed region denuded of surface epithelium. The surface epithelial cells at the edges were degenerated. The stroma was densely packed as a result of involution with loss of intercellular fluid. Numerous large sinuses were present. Projecting into the cavity of the uterus from this region were masses of erythrocytes, intercellular fluid, and some tissue fragments.

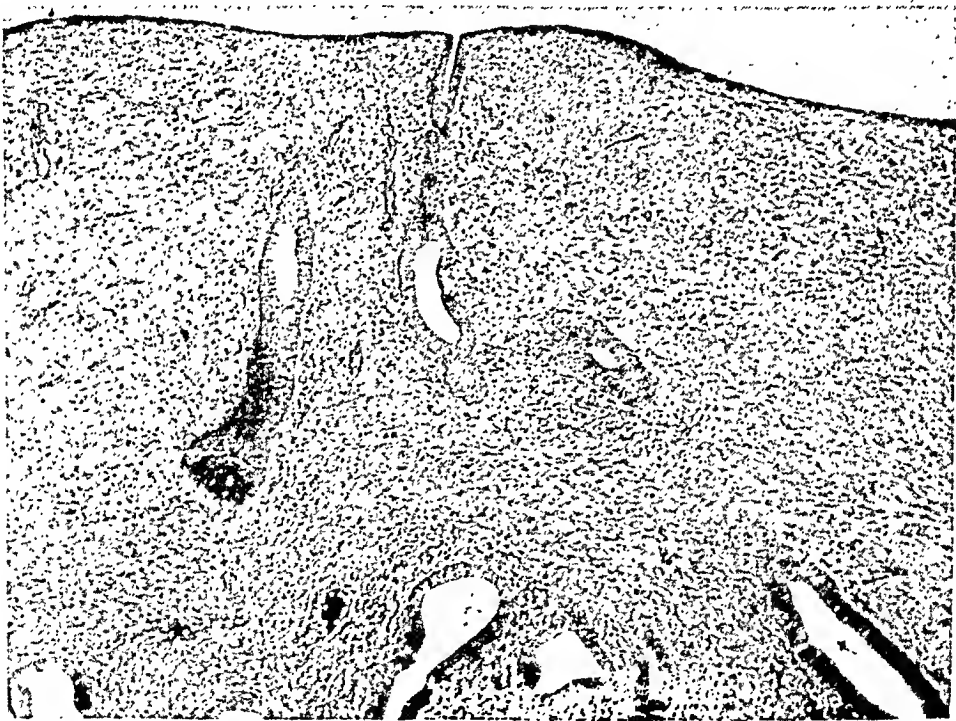


Fig. 10.—Specimen No. 293. This portion of the endometrium is typical of an immediate postmenstrual type. Irregular shedding characteristics are shown in Figs. 9 and 10. Prolonged activity of the corpus luteum (Fig. 8) is the direct cause of such endometrial tissue reactions.

In other regions the endometrium was typically post menstrual in type (Fig. 10). The intact surface epithelium in some places was columnar, in others cuboidal, and in still others was flattened. The glands were straight and had tall columnar epithelium without evidence of secretory activity. Mitoses, while present, were not numerous. The stroma was loosely arranged, and the spindle-shaped cells were small.

Interpretation: The corpus luteum had remained in the postvascular stage for a prolonged period of time, and, though small, maintained functional activity as indicated by the secretory character of the endometrium.

Some regions of the endometrium were still intact and secretory in character, while other regions had sloughed and had been completely repaired, although other portions continued to bleed.

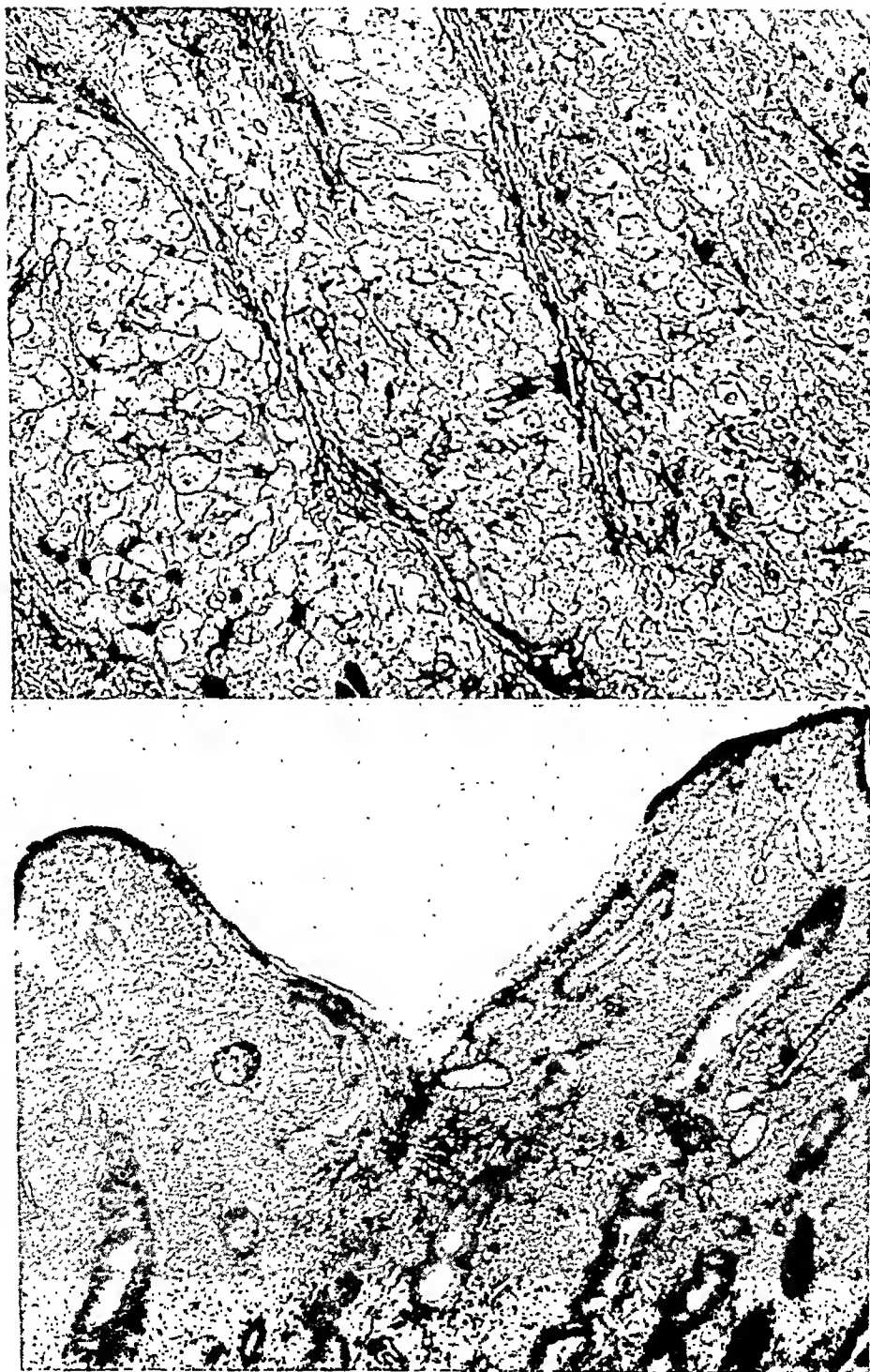


Fig. 11.—Specimen No. 265. On day 11 of continuous uterine bleeding most of the granulosa cells have degenerated but a few still retain mature characteristics. The life cycle of this corpus luteum has been prolonged.

Fig. 12.—Specimen No. 265. Some regions of the endometrium yet unhealed appear to be undergoing repair. The general picture is that of the final stage of prolonged bleeding just before the completion of healing. The histology of the corpus luteum (Fig. 11) is consistent with

This specimen demonstrates the wide range of endometrial variation that may occur with irregular shedding in instances of functional uterine bleeding associated with prolonged life and function of a corpus luteum. The inability of recently regenerated endometrium to respond to corpus luteum stimulation was also shown.

SPECIMEN No. 265.—Aged 38 years; gravida 0; unmarried; operated on day 11 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight-day cycles with four to five days flow. During the ten years prior to operation the flow became longer and more profuse, and the cycles became shorter and irregular. A period of bleeding began June 6, 1939, and continued through July 20, 1939. On Aug. 13, 1939, bleeding began again and, when operated upon on August 23, 1939, bleeding was still present.

Operation: Hysterectomy and resection of corpus luteum.

Pathologic diagnosis: Uterus (no gross pathologic lesions of uterus, tubes, or ovaries were demonstrated).

Corpus luteum: The corpus luteum prior to fixation was 0.4 by 0.4 by 0.3 cm., had a wavy yellow wall, and a hemorrhagic centrum. The granulosa lutein cells in most regions evidenced marked degeneration. In many places these cells had been replaced by connective tissue. In some small regions the granulosa lutein cells were intact, shrunken, had evenly stained cytoplasm, and round or oval well-stained nuclei (Fig. 11). Such cells were not usually found in corpora lutea during this phase of a normal cycle. There was a marked ingrowth of connective tissue, and the border about the central cavity was dense, thick, and well organized. The theca cells were intact and evidenced little degenerative changes.

Endometrium: The fixed and stained endometrium was as thick as 0.3 cm. The stroma was loosely arranged, had considerable edema, and the cells were spindle shaped. The glands were straight, and were lined by tall columnar nonsecretory epithelium. Abundant epithelial cells in mitoses were present. Mitoses in stroma cells were frequent. These findings indicated active growth. These above findings were uniformly present throughout the endometrium, except for a few small regions where the surface epithelium was lacking. One such region was depressed below the level of the adjacent surface epithelium (Fig. 12). Its surface was irregular, and was covered with a narrow layer of blood cells. This represented a yet unhealed and still bleeding region. In another region not covered with epithelium there was a small mass of erythrocytes projecting above the surface and extending down into the stroma where it was continuous with a blood-filled sinus. The blood had escaped from a break in the wall of the sinus.

Interpretation: The corpus luteum was almost completely regressed from both a histologic and functional standpoint.

The endometrium was repaired in most portions, while in some the healing was incomplete. It is interpreted that healing would shortly have been complete.

The bleeding originated in the regions of delayed and incomplete healing of the endometrium, and was not typical of the normal menstrual processes.

This represents the terminal phase, immediately prior to completion of endometrial repair, of the prolonged life of the corpus luteum and of irregular regression of the endometrium.

SPECIMEN No. 257.—Aged 31 years; para iii, gravida v; operated on day 1 of bleeding.

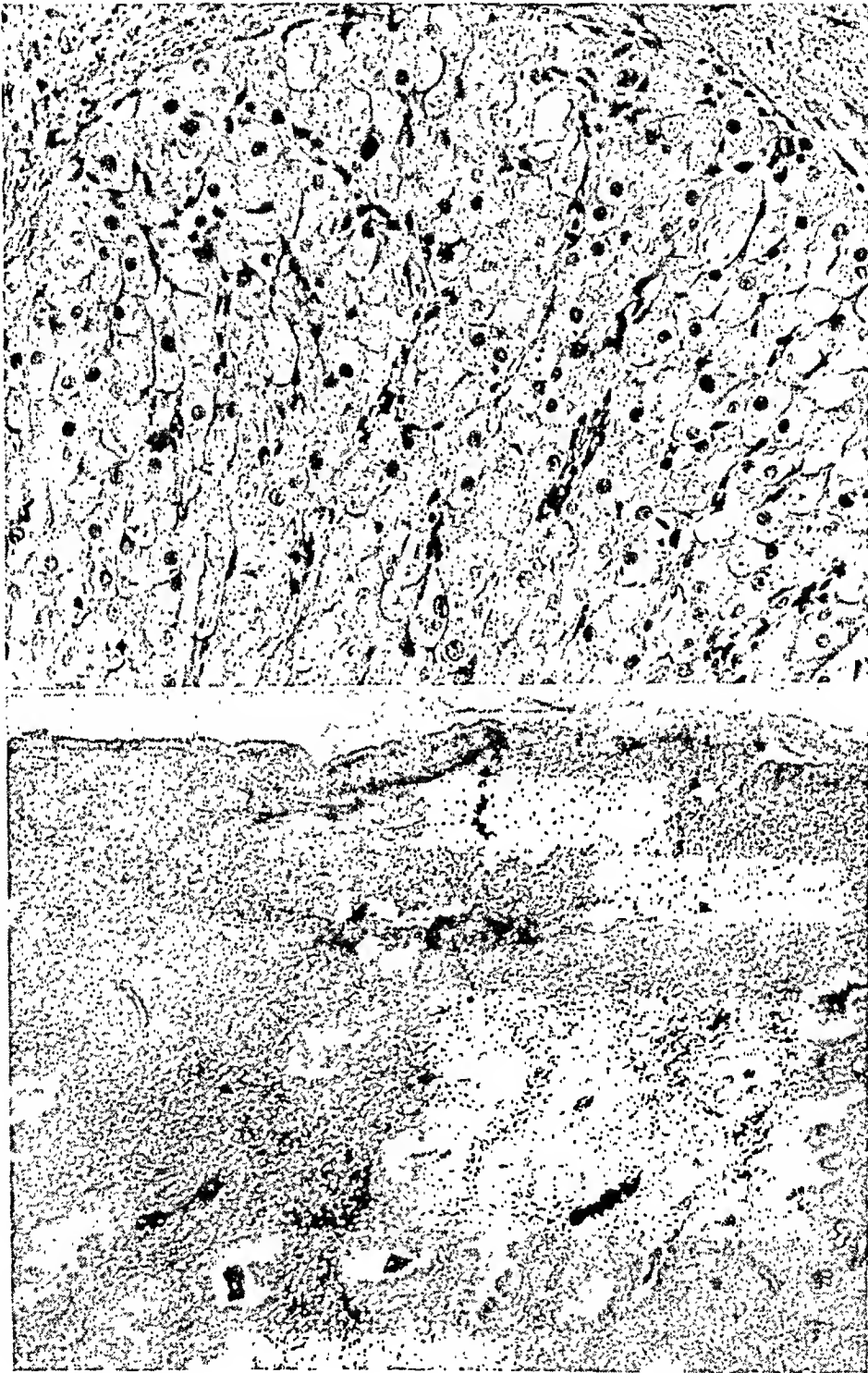


Fig. 13.—Specimen No. 257. This corpus luteum in the postvascular stage is functioning normally as indicated by the secretory character of the endometrium (Fig. 14). Ovulation in this patient must have occurred during a prolonged period of uterine bleeding.

Fig. 14.—Specimen No. 257. The endometrium has responded normally to corpus luteum stimulation. In a few regions the surface epithelium is disrupted, and bleeding is occurring from large venous sinuses immediately beneath the surface. The bleeding mechanism seems independent of the tissue changes of the endometrium, and also of the corpus luteum stimulation or withdrawal of stimulation.

Menstrual history: Onset at 12 years of age; twenty-eight-day cycles, with three to four days flow until six years prior to operation. During these six years the cycles were irregular, both too short and too long, and the bleeding phase lasted eight to ten days. On Oct. 12, 1938, a dilatation and curettage were done for diagnosis, and in an attempt to stop the bleeding. Bleeding ceased for three weeks after the dilatation and curettage, and then on Nov. 2, 1938, bleeding began again and continued until Dec. 15, 1938. On Dec. 22, 1938, bleeding began, and on that day a hysterectomy was performed.

Operation: Hysterectomy, left salpingo-oophorectomy.

Pathologic diagnosis: Uterus, tube, and ovary.

Corpus luteum: The corpus luteum prior to fixation was 2 by 1.5 by 1.5 cm. It had a wide yellow wall and a hemorrhagic centrum. Many of the granulosa lutein cells were shrunken, had irregular cell membranes, pyknotic nuclei, and vacuolated cytoplasm. Other cells retained their large size, had evenly stained cytoplasm, and round or oval nuclei (Fig. 13). The majority of cells, however, showed shrinkage in size. There was a moderate amount of connective tissue throughout the granulosa lutein and along the inner border. The blood vessels in most regions were empty and collapsed. Some occasional regions, however, had dilated blood-filled vascular spaces. In these regions cell degeneration was less evident.

Endometrium: The endometrium after fixation and staining was as thick as 0.45 cm. The glands were typical of the full secretory type (Fig. 14). They were large, serrated, had large cells with secretory vacuoles peripherally, and contained secretion in their lumens. The stromal cells were large, compactly arranged, and resemble predecidua. Spiral arteries reached to the surface epithelium. Involution had occurred.

There were some regions in which there was no surface epithelium. The epithelial cells at the edges of these gaps were degenerated. Filling the denuded regions and extending into the cavity of the uterus from large disrupted venous sinuses were masses of blood cells with some fibrin. These regions represented bleeding zones. The desquamation of endometrium was practically nil except for loss of surface epithelium. The large venous sinuses lay parallel to the surface.

Interpretation: The corpus luteum was histologically normal and was comparable to a postvascular, regressing stage (day 24 to 26). That its function was normal was indicated by the normal full-blown secretory character and the stromal response of the endometrium.

The endometrium in most regions had responded normally to estrogenic and progesterone stimulation.

The bleeding was not typical of normal menstruation since there was only disruption and bleeding from vascular sinuses without tissue loss to any extent.

Ovulation must have occurred during a period of bleeding and corpus luteum development progressed normally during bleeding.

The bleeding mechanism seemed independent of ovarian function.

SPECIMEN No. 266.—Aged 31 years; para iii, gravida iii. Operated on day 16 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight-day cycles, with three days flow until the patient was 30 years of age. During the last year prior to operation the bleeding periods were profuse and lasted ten to fourteen days. There was also some intermenstrual spotting of blood. Bleeding began sixteen days prior to operation and had continued.

Operation: Complete vaginal hysterectomy, resection of corpus luteum.

Pathologic diagnosis: Small uterine myomas (tubes and ovaries normal).

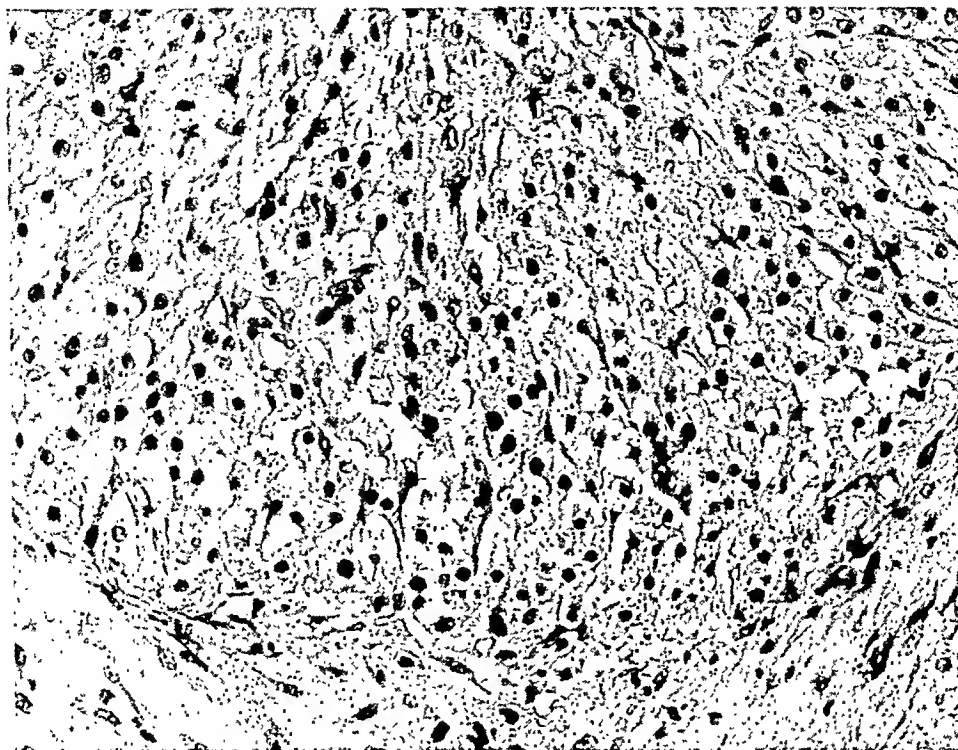


Fig. 15.—Specimen No. 266. The corpus luteum is young and is of the new cycle. The response of the endometrium (Fig. 16) to progesterone is consistent with the degree of development of the corpus luteum. Ovulation must have occurred during the sixteen-day period of uterine bleeding.

Fig. 16.—Specimen No. 266. The endometrium is early secretory in character. Independent of this normal tissue response certain small superficial regions of endometrium are bleeding. Desquamation is minimal. The bleeding seems independent of the corpus luteum and the general normal endometrial tissue response to stimulation.

Corpus luteum: The corpus luteum measured 2 by 1.5 by 1.2 cm. prior to fixation and had a wavy yellow wall. The granulosa lutein cells were not large, but in most regions were definitely luteinized. Many of the cells were vacuolated. There was extravascular blood scattered between the cells of this layer. In some places the cells were not yet luteinized, were elongated, and were arranged in streamerlike fashion. Along the inner margin the cells retained the granulosa cell characteristics, were not luteinized, were highly vacuolated, and had pyknotic nuclei. The ingrowth of connective tissue was scant in the granulosa lutein layer. A meager amount of connective tissue projected into the central cavity (Fig. 15).

Endometrium: The endometrium after fixation and staining was as thick as 0.4 cm. In all but a few small places the endometrium was covered with surface epithelium. The glands were similar throughout entire endometrium. They were slightly tortuous. The gland cells were columnar, had centrally located nuclei, and contained secretory vacuoles both in the basal and peripheral portion of the cells (Fig. 16). The loosely arranged stromal cells were spindle shaped and were widely separated by intercellular fluid. One of the regions void of surface epithelium was depressed below the general surface level, and was irregular. Projecting into the cavity of the uterus from this region were erythrocytes, edema fluid, and a small amount of stromal tissue elements.

Interpretation: The corpus luteum was young, was of the new cycle, and its development had progressed normally. Ovulation and corpus luteum development had occurred during a period of active bleeding.

The endometrium had responded normally for the most part to corpus luteum stimulation. The bleeding portion of the endometrium was neither in keeping with the remainder of the endometrium nor with the development of the corpus luteum.

The bleeding mechanism appeared to be independent of the corpus luteum function or failure of function.

SPECIMEN No. 273.—Aged 31 years; para iii, gravida v; operated on day 60 of bleeding.

Menstrual history: Onset at 15 years; twenty-eight-day cycles, with five days flow until two months prior to operation when she began to flow and flowed continuously to time of operation. At times this was only a spotting, and at times was profuse.

Operation: Hysterectomy and resection of corpus luteum from ovary.

Pathologic diagnosis: Multiple small uterine myomas.

Corpus luteum: The corpus luteum after fixation and staining was 1.1 cm. in diameter. There was a marked folding of the wall, considerably more than usually observed. The granulosa lutein cells were large, stained evenly, and had large round or oval nuclei (Fig. 17). Few cells evidenced regressive changes. There was moderate ingrowth of connective tissue. The connective tissue border of the central cavity was thin and loosely arranged. The blood vessels throughout the granulosa lutein layer contained few erythrocytes.

Endometrium: The endometrium after fixation and staining was as thick as 0.3 cm. The glands were somewhat tortuous. There was no secretion in their lumens. The gland cells were tall columnar with centrally placed oval nuclei. At the base of the cells there were large secretory vacuoles (Fig. 18). No cells in mitoses were found in a study of several sections from different blocks. The stromal cells were small and were widely separated by intercellular fluid. Spiral arteries did not reach to the surface.

One small portion of the endometrium had no surface epithelium. Extending into the uterine cavity through this denuded region was a large mass of

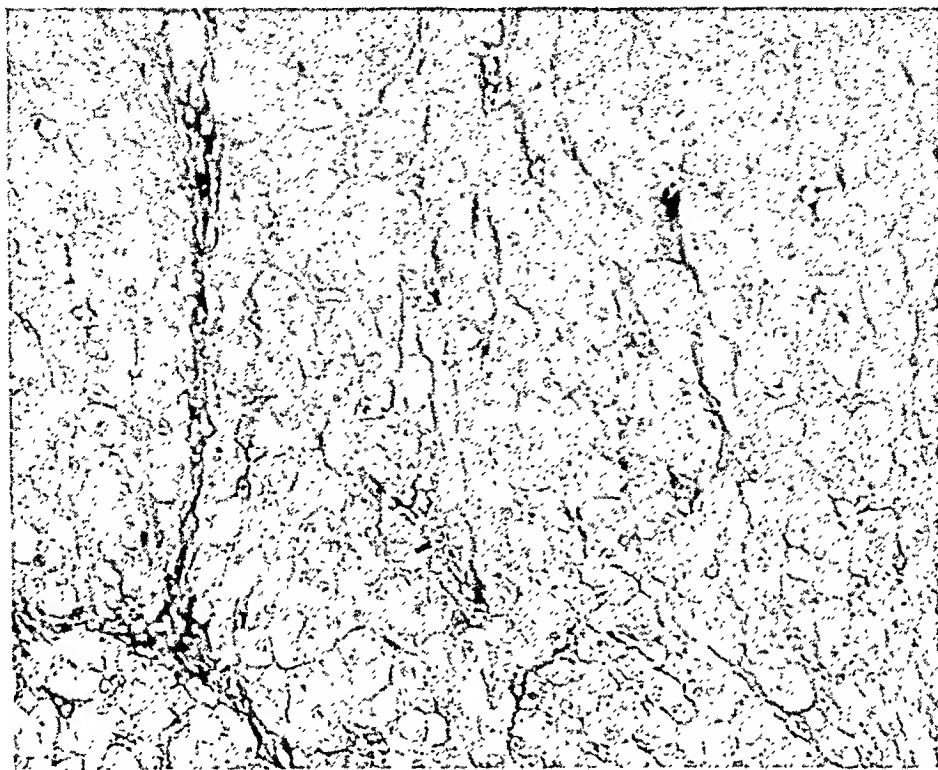


Fig. 17.—Specimen No. 273. This corpus luteum was removed from a patient who had been bleeding continuously for two months. It is functionally active. The relationship of the corpus luteum and the endometrium indicate that ovulation had occurred and corpus luteum development had continued during a period of prolonged uterine bleeding.

Fig. 18.—Specimen No. 273. The endometrium, except in a few small superficial regions, is typical of the early secretory stage. Bleeding is occurring from these regions. Desquamation of tissue is scant and is unlike normal menstruation. The bleeding mechanism seems independent of the general endometrial reaction and the corpus luteum.

intercellular stromal fluid. At the base there was some extravasated blood and a small amount of fibrin.

Interpretation: During the bleeding phase the endometrium had desquamated, bled, repaired itself, and had responded for the most part to the stimulation of the corpus luteum of the new cycle. One region was still not healed. The fact that the endometrium evidenced less change than anticipated by the appearance of the corpus luteum is explained on the basis that the endometrium was recently regenerated and consequently was not able to respond fully as yet.

Ovulation and corpus luteum development must have occurred and progressed normally during the period of bleeding.

It is indicated that the bleeding mechanism is independent of the corpus luteum function or failure of function.

SPECIMEN No. 375.—Aged 30 years; para 0, gravida i; operated on day 20 of cycle; day 1 of bleeding.

Menstrual history: Onset at age of 14 years; twenty-eight day cycles with five days flow until one year before operation. During that year the cycles were twenty-five days in length with a profuse flow for eight days. Last menstrual period was Feb. 1, 1941. Operated on February 20. Began to bleed February 19.

Operation: Hysterectomy and bilateral salpingo-oöphorectomy.

Pathologic diagnosis: Multiple uterine fibroids and residues of pelvic infection.

Corpus luteum: The corpus luteum prior to fixation was 1.5 cm. in diameter. The granulosa lutein cells were luteinized, but were not yet large (Fig. 19). The granulosa cells nearest the source of blood supply were larger and more fully luteinized than those cells near the inner border. In the inner region of the corpus luteum the granulosa lutein cells were elongated as in young corpora lutea. In many regions these cells were separated by extravascular blood. This was particularly prominent near the inner border of the granulosa lutein cell layer. There was a moderate ingrowth of connective tissue, and the cells projected into the central cavity. The vascular structures in the layer are filled with blood. Chemical analyses of phospholipids and cholesterol esters (Weinhouse¹⁴) of one-half of the corpus luteum revealed values, expressed in per cent of moist weight of tissue, of 1.38 and 0.11, respectively.

Endometrium: The endometrium after fixation and staining was as thick as 0.53 cm. The glands were tortuous and had secretion in their lumens. The gland cells were large, had large oval nuclei located toward the bases of the cells, and contained secretory vacuoles in the peripheral portions. Many of the gland lumens contained blood. The closely arranged stromal cells were large and had oval nuclei. Most of the endometrium was of this character and was covered with epithelium. Involution had occurred and there was a superficial extravasation of leucocytes and lymphocytes (Fig. 20). Vaginal examination prior to operation revealed blood in the vagina and cervical canal. Gross examination of the endometrium at the time the uterus was surgically removed revealed one small bleeding region in the endometrium in the lower portion of the uterus. A block of tissue including this region was taken (Fig. 21). In the vicinity of this bleeding region the stroma was compact; there was a superficial infiltration of lymphocytes and leucocytes; and there was some localized extravasation of erythrocytes. The glands were straight and the gland cells showed no evidence of presently existing secretory activity. In the lumens of a few of the glands, however, there was some secretion indicating that some of the glands had had an antecedent secretory activity. The bleeding region itself was characterized by a loss of surface epithelium, marked hemorrhage in the underlying super-

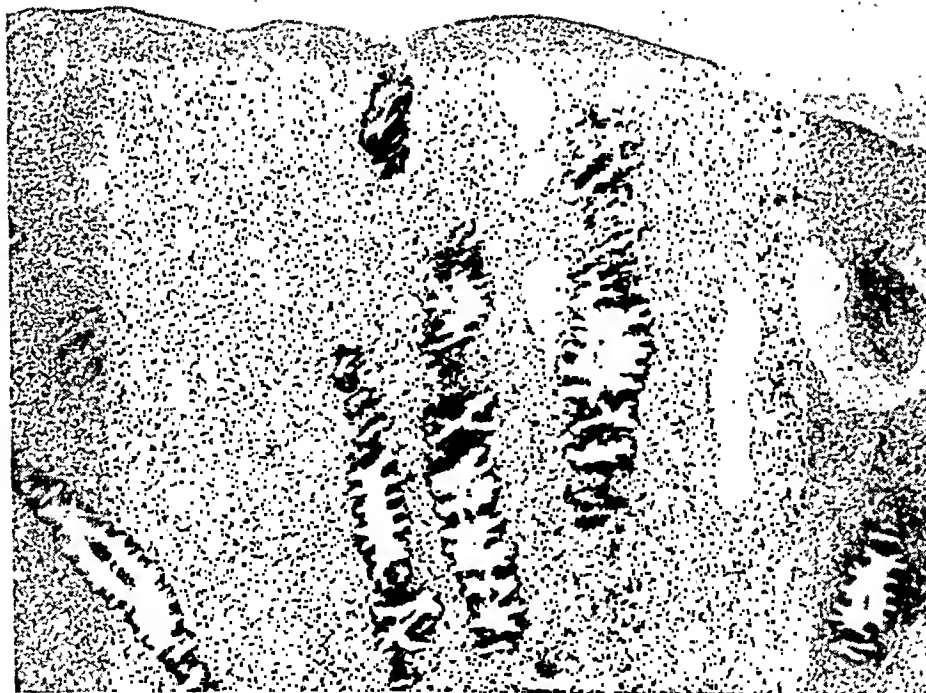
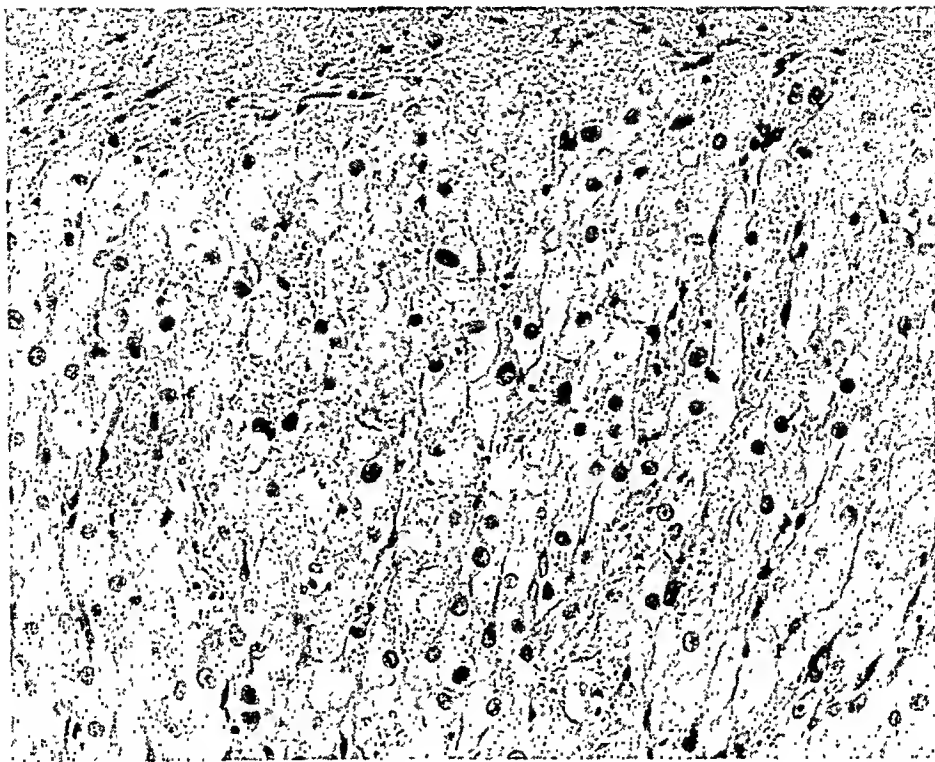


Fig. 19.—Specimen No. 375. The corpus luteum is young and is normal.

Fig. 20.—Specimen No. 375. This portion of the endometrium has responded to progesterone stimulation to a greater degree than the development of the corpus luteum (Fig. 19) would indicate. Involution and other changes incident to bleeding have occurred.

ficial stroma, and desquamation of tissue. Hemorrhage and tissue fragments projected into the cavity of the uterus. The actual loss of tissue was not great.

Interpretation: The corpus luteum was young and was consistent with a normal day 20 of the cycle. Chemical analyses of the corpus luteum indicated normal functional activity of a young corpus luteum of this histologic age.

Most of the endometrium was typical of an endometrium immediately prior to the onset of flow. It was of the type usually associated with a mature corpus luteum of greater age than the corpus luteum found here.

Bleeding was occurring from the endometrium, although the corpus luteum was young, and development was progressing normally. The involution, desquamation, and bleeding phenomena of the endometrium were similar to that observed in normal menstruation.

In this specimen the bleeding mechanism and endometrial tissue reaction seemed independent of the corpus luteum function or failure of function.



Fig. 21.—Specimen No. 375. Desquamation and bleeding are taking place in this localized region. Some of the glands evidence little secretory activity. The advanced degree of endometrium stimulation (Fig. 20), the involution, desquamation and bleeding are not consistent with the stage of development of the normal functioning corpus luteum (Fig. 19).

Discussion

In all of the specimens presented here the bleeding was from an endometrium which was progestational in type. A corpus luteum was present in the ovary in each instance. The relationships of the corpus luteum and the endometrium were not the same in all the specimens. There were two distinct types. In one group the corpus luteum appeared to vary from the normal. The abnormality consisted of a prolongation of life and function of the corpus luteum.

In response to the abnormal corpus luteum stimulation, the endometrium evidenced characteristic changes that have been described previously as "irregular shedding," "irregular regression," and "mixed type."

In the second group the corpus luteum and its functional activity appeared normal. The endometrium evidenced normal responses to the corpus luteum stimulation except in small localized regions. It was from these localized regions which have failed to respond that the bleeding occurred.

For the sake of convenience the specimens, accordingly, shall be grouped and discussed in that sequence.

Prolonged life of the corpus luteum in the form of a corpus luteum cyst has been frequently described. The life and function of the corpus luteum, however, may be prolonged without alteration of gross characteristics from the normal and without cyst formation. Direct evidence of this obtained by studies of corpora lutea themselves have been few, but evidence obtained by less direct means is quite conclusive. The evidence has been accumulated from endometrial specimens and biological assays of patients with functional uterine bleeding associated with a progestational type of endometrium. The endometrium in these instances is described as "irregular regression or shedding," and "mixed" type (Meyer;² Traut and Kuder;³ McKelvey;⁴ McKelvey and Samuels;⁷ and Jones⁶). That the life of the corpus luteum is prolonged in such instances is indicated by several studies. McKelvey and Samuels⁵ report the presence of pregnandiol in the urine of patients during the period of bleeding from such an endometrium. This indicates that progesterone secretion is continuing. Normally pregnandiol is not found during a bleeding phase. The endometrial gland cell and stromal tissue responses are those observed only as a result of progesterone stimulation. Holmstrom and McLennan⁷ produced the characteristic picture of "irregular shedding" with prolonged bleeding by giving injections of progesterone during the bleeding phase of the cycle of normally menstruating women, thus proving that prolonged secretion of progesterone can reproduce the endometrial changes and the prolonged bleeding.

In the present study microscopic characteristics of the corpus luteum during various stages of its prolonged life are described. These findings confirm the evidence noted above. The earliest phase in the cycle in which we observed undoubted prolongation of life of the corpus luteum was in a specimen (No. 335) obtained near the onset of bleeding. The duration of the bleeding period in this patient had in the past been prolonged to eight days. The corpus luteum (Fig. 1) was maintained in the vascular stage with but little evidence of degeneration on day 27. That bleeding was about to begin was indicated by the occurrence of involution of the endometrium (Fig. 2) and small local superficial regions of extravasation and desquamation (Fig. 3). Our study of many human specimens warrants the statement that such a corpus luteum as this is not normally found in this stage of the cycle. It also justifies the contention that such a corpus luteum as this would not regress immediately, but rather would degenerate over a period of several days.

Specimen No. 332 obtained on day 14 of bleeding showed such a picture. In some regions the granulosa lutein cells evidenced but few regressive changes

such as reduction in cell size associated with an increase of connective tissue throughout the layer (Fig. 5). The granulosa lutein cells appeared histologically similar to functioning cells. Other cells showed more regression, but none evidence more degeneration than was frequently observed in specimens obtained on day 1 to 5 of normal menstruation (Fig. 4). This "irregular" regression of the corpus luteum was an exaggeration of the normal. In normal menstruation on day 1 there were considerable variations in different portions of the same corpus luteum as well as in different corpora lutea (Brewer and Jones⁸). In normal menstruation, however, a corpus luteum is not maintained in such an intact state as this for fourteen days after the onset of bleeding. That the corpus luteum had continued to function is shown by the presence of some secretory glands in the endometrium (Fig. 7). Thus, the interpretation of function from the histologic picture of the granulosa lutein cells is accurate. Other glands in this still bleeding endometrium had regressed or had desquamated in part and were of the postmenstrual type (Fig. 6).

This specimen indicates without doubt that prolonged life and function of the corpus luteum does occur; that its regression, when it occurs, does so slowly and in an irregular way; and that it is a basic and fundamental part of so-called "irregular regression" of the endometrium and functional bleeding from a progestational endometrium. Irregular regression of the endometrium in reality is only an expression of the abnormality of the corpus luteum.

Another specimen, No. 334 obtained on day 8 of bleeding, had a corpus luteum which had persisted without much evidence of degeneration. It was large (1.5 cm.), was still vascularized, the granulosa lutein cells were intact, and the connective tissue throughout the layer and bordering the central cavity was scant. The endometrium in most regions contained glands that were secretory in type. Those portions of the glands that had not been desquamated were regressing. Desquamation seemed to have almost been completed. In other regions the endometrium was of the usual postmenstrual type, and was covered with surface epithelium. Regeneration had completed itself in some portions of the endometrium during the bleeding period, and it was more advanced than in the previous specimen. The prolonged life and function of the corpus luteum was apparent, since such findings as these are not present in normal menstruation. Irregular and prolonged regression of the endometrium occurred as a direct response to the irregular and prolonged degeneration of the corpus luteum. Prolonged bleeding is a natural sequence.

McKelvey⁴ observed that the longer the duration of bleeding the greater the variation in the endometrial pattern. Specimen No. 293 obtained on day 45 of bleeding confirms that observation. The endometrium in one portion was thin, was covered with intact surface epithelium, and contained glands that evidenced active secretory function (Fig. 9). The stroma was unusual in that there was a great amount of intercellular fluid. Other portions of the endometrium were desquamated, bleeding, had few glands, dense stroma, and contained many large blood sinuses (Fig. 9, arrow). Still other portions were intact, were covered with a newly regenerated epithelium, and had straight, nonsecretory, postmenstrual type of glands (Fig. 10). This region gave the

appearance of having sloughed and having regenerated completely, while other portions of the endometrium continued to bleed and desquamate, and still others remained in a state of secretory activity without slough or bleeding.

The associated corpus luteum was small, but it was typical of a postvascular stage from a histologic standpoint (Fig. 8). Although most of the granulosa lutein cells were small, they resembled functioning cells. That they still retained functional capacity was evidenced by the secretory character of the endometrium. The life of the corpus luteum in this instance had been prolonged in the regressive stage, and a slow irregular shedding of the endometrium had resulted. This specimen also clearly demonstrates the fact that recently regenerated endometrium is not able to respond to corpus luteum stimulation, and that a phase of growth is necessary prior to participation in mature function, namely, secretory activity and preparation for an implantation site.

Near the termination of a bleeding phase in this particular type of functional uterine bleeding there are certain typical findings. Specimen No. 265 obtained on day 11 of bleeding consisted of a small corpus luteum in which many of the granulosa lutein cells were degenerated, but a few granulosa lutein cells still retained their large size, even staining cytoplasm, intact cell membranes, and round or oval nuclei (Fig. 11). These cells, however, represent but an extremely small portion of the granulosa lutein layer. The picture in general is one of degeneration. The functional capacity of such a corpus luteum is nil. The life cycle of the corpus luteum, however, has obviously been prolonged, since cells such as those described are not present in corpora lutea of normal menstruation eleven days after the onset of bleeding.

The endometrium had been repaired in all except a few small regions, and was typical of a proliferative phase. A region still denuded of surface epithelium had the appearance by its surface contour of a zone in which healing would take place shortly (Fig. 12). The irregular shedding phase was represented in this late phase only by such still unhealed regions which still bled. The life of the corpus luteum had been prolonged, but regression was completed, and the endometrium had repaired itself and was developing for the next cycle. The endometrium not involved in the local bleeding regions had responded normally, and was consistent with a normal proliferative phase.

These specimens would indicate that abnormal or functional uterine bleeding does occur from an endometrium that evidences progestational characteristics. They indicate, as far as the pelvic organs are concerned, that the corpus luteum life cycle is altered from the normal in that its life and function are prolonged. As a result the endometrium is shed in an irregular way, a mixed pattern occurs, and the desquamating and bleeding phase is prolonged. As slough in one local region is completed, healing takes place, and that region of endometrium begins development, irrespective of the character of the other regions. Local variations in responses occur in the endometrium in normal menstrual cycles (Bartelmez;⁹ Brewer and Jones⁸), and it is only an exaggeration of this that is observed in this type of functional uterine bleeding. The corpus luteum in normal menstruation may, and frequently does, vary in dif-

ferent regions (Brewer and Jones⁸). Some cell regions evidence degeneration, and others do not. In functional uterine bleeding these variations may be exaggerated. Persistence of the corpus luteum in a certain phase for a longer time than usual, and prolongation of the degeneration phase seem to be the common phenomena observed in patients who have this particular type of abnormal bleeding from a progestational endometrium. The direct cause of the alteration of the life cycle is undoubtedly the pituitary, which in itself may or may not be the primary factor.

In this type of bleeding associated with irregular shedding of the endometrium, the bleeding and desquamation are similar to and are an exaggeration of the normal processes of menstruation.

Irregular shedding is not in itself an entity as advocated by some, but rather is only a part of a more general endocrine disturbance. The primary cause is not proved, but without doubt the corpus luteum and pituitary gland are involved.

The second group of corpus luteum endometrial relationships observed in patients with functional uterine bleeding from a progestational endometrium is composed of those specimens in which the corpus luteum cycle is normal, the endometrium responds normally, and the bleeding phenomena seem to be independent of the corpus luteum or the type of the endometrium.

The corpus luteum of Specimen No. 257 is of the postvascular early regression type (Brewer¹⁰), or the so-called bloom stage of other authors (Fig. 13). The endometrium, except in small regions, is consistent with this stage of life of the corpus luteum (Fig. 14). There is a normal relationship between these two tissues. This specimen was obtained on day 1 of bleeding, but a six weeks period of bleeding had just terminated seven days before the new bleeding started on the day of operation. Ovulation must have occurred during this previous period of bleeding, since the corpus luteum is older than seven days. In spite of the bleeding the normal mechanism of ovulation and corpus luteum development occurred, indicating that the hormonal balances and actions were within normal limits. The endometrium, for the most part, had developed and responded in the usual normal manner to corpus luteum stimulation. The relationship of these two tissues from the standpoint of secretory development and activity appeared normal. Portions of the endometrium, however, were bleeding. The bleeding was from large sinuses lying just beneath and parallel to the surface (Fig. 14). The surface epithelium was denuded, and active bleeding was in progress. The normal desquamation was lacking. The independence of this bleeding from the corpus luteum was apparent. The processes by which it was brought about were not determined.

Specimen No. 266 was obtained on the sixteenth day of continuous bleeding. The corpus luteum was young and from its histologic characteristics ovulation must have occurred during the sixteen-day period of continuous bleeding (Fig. 15). The major portion of the endometrium had responded to corpus luteum stimulation in a normal manner (Fig. 16). The early secretory type of glands and stromal reaction were consistent with the histologic picture of the corpus luteum. This suggests that the corpus luteum function corresponded

to its histologic development. One superficial region of the endometrium, however, was at variance with the general over-all picture (Fig. 16). The surface epithelium was lost; there was a scant superficial desquamation of the underlying stromal tissues; and blood and intercellular stromal fluid projected into the uterine cavity. This local region was at complete variance with the degree of development of the corpus luteum and endometrium. Since the corpus luteum and endometrium generally had reacted normally from an endocrine and tissue response standpoint, it can only be concluded that the localized bleeding was independent of corpus luteum control or function. This bleeding did not effect the normal response of the remainder of the endometrium. The explanation of the mechanism cannot be made, but its independence was apparent.

Specimen No. 273 was obtained on the sixtieth day of continuous bleeding. Ovulation in this specimen must have occurred during this period of bleeding, and the development of the corpus luteum progressed normally in spite of the bleeding. The corpus luteum was in the immediate postvascular stage (Fig. 17). That it was functioning was indicated by the histologic picture of the endometrium which showed progesterone stimulation. The development of secretory activity of the gland cells was less than would be anticipated normally, but this was probably due to the fact that the endometrial response was somewhat retarded due to recent regeneration. One region was denuded of surface epithelium, and slight bleeding was occurring (Fig. 18). There was scant desquamation of the tissue, and the depressed surface was quite regular. There was a complete independence of the tissue reaction in this region from the remainder of the endometrium which was normal. There was likewise no evidence that this region has any close relationship to the corpus luteum function, but rather it appeared completely independent. The bleeding seemed to be the result of some local fault in the endometrium, and appeared to be independent of corpus luteum function or failure of function.

That the bleeding may be a part of a mechanism that is independent of the ovary is not a new thought. It was stated by Bartelmez⁹ that "variations in the endometrium in menstruation point toward the relative independence from the ovary of the vascular control of the uterus." In a recent study of corpus luteum-endometrial relationships at or near the onset of normal menstruation, the impression was gained that the bleeding phenomena did not correlate well with the histology of the normal corpus luteum (Brewer and Jones⁸). Traut and Kuder³ were impressed with the independence that the mechanism of endometrial blood loss may show of the factors controlling tissue change. The second group of specimens reported here had endometrial tissue changes that are consistent with the histology and functional activity of the corpus luteum, but the bleeding is at variance and has no apparent relation with the corpus luteum. The bleeding in these specimens of the second group is not typical of normal menstrual slough and bleeding, but rather the bleeding seems to be from vascular sinuses without much tissue loss or local tissue reaction, such as involution, extravasation, and infiltration of leucocytes and lymphocytes. Hamblen¹¹ noted in cyclic bleeding associated with menorrhagia and a secretory type of endometrium that the bleeding in general was not characterized by tissue loss in the

endometrium as in normal menstruation. Jones⁶ observed normal premenstrual tissues in eight patients in whom active bleeding had been going on up to thirty-four days, and stated that apparently the bleeding was occurring from an endometrium which was not being shed to the extent that occurred in normal menstruation. This type of bleeding is exemplified by specimen No. 257. Watson¹² noted free bleeding from the vascular bed in instances associated with continued secretion of progesterone. Kurzrok¹³ observed that bleeding beginning at ovulation may continue up to menstruation, that the endometrium is in the secretory phase, and that the endometrium increases normally in development, irrespective of the continued bleeding. Our Specimens No. 257, No. 266, and No. 273 demonstrate this. Kurzrok felt that the factors responsible for the bleeding were not dependent upon the histologic type of the endometrium. We would like to go farther and say that in this particular type of functional uterine bleeding the factors responsible are not dependent upon either the histologic type of the endometrium or the corpus luteum.

From a study of these tissues, it is apparent that ovulation may occur during a period of abnormal bleeding, that corpus luteum development may progress normally, and that the endometrium may respond normally and continue to develop normally. If the bleeding were the result of abnormal endocrine factors, it is hard to explain why all these other normal tissue developments, both from a histologic and endocrine standpoint, should continue to maintain. The only possible conclusion is that the bleeding mechanism in such instances is independent of the function of the corpus luteum. That the factor responsible resides within the endometrium proper as Kurzrok suggested is entirely possible. That the endometrium cannot respond normally to normal stimulation may be a factor in the causation of this type of bleeding. This factor has not been given adequate consideration primarily because it is difficult to prove.

One specimen (No. 375) suggests that abnormal responses of the endometrium can be primary in causing functional bleeding in some instances. The specimen was obtained on day 20 of the cycle, yet abnormal bleeding had begun late in the day on day 19. At the time of operation, bleeding had been in progress for less than twenty-four hours, so this is termed a day 1 case of functional uterine bleeding. The corpus luteum is histologically normal and is in every way comparable to a young corpus luteum that might be obtained on day 20 of a normal twenty-eight day menstrual cycle (Fig. 19). That its function is normal was determined by chemical analysis of one-half of the corpus luteum (Weinhouse and Brewer¹⁴). The phospholipid and cholesterol ester values expressed in per cent of moist weight of tissue were respectively 1.38 and 0.11. These values are comparable with those obtained in corpora lutea of the same age of normal menstrual cycles. The phospholipids indicate functional activity of the tissue, and the low cholesterol ester values indicate that degeneration has not occurred, since these values are high during degeneration (1.25 in day 1 cases, Weinhouse and Brewer¹⁴). The endometrial responses, however, did not correspond in degree of development and activity to that of the corpus luteum. The glands in most regions were stimulated to a degree far greater than anticipated. Involution had occurred, and there was a super-

ficial extravasation of lymphocytes and leucocytes indicative of impending menstruation (Fig. 20). In one localized portion desquamation and bleeding had occurred (Fig. 21). In this region the glands were simple and showed little evidence of active or antecedent secretory activity. This may be the direct result of involution, or it is possible the gland cells did not adequately respond to stimulation. No other luteinized tissue was present in the ovaries. Both ovaries were removed, and careful search revealed none. The endometrium had not responded in the usual way to corpus luteum stimulation. The tissue changes incident to bleeding were similar to those observed in normal cycles. These characteristic changes, however, are usually found in association with a mature corpus luteum that evidences regression. Here the corpus luteum was young and, from a histologic and chemical analysis standpoint, was functioning normally. An explanation of this relationship between the corpus luteum and endometrium is difficult, since it does not correspond to anything that we have observed in abnormal or normal uterine bleeding. The abnormal reaction of the endometrial tissue in the presence of a normal corpus luteum suggests that in this instance the factor or factors that initiate bleeding reside within the uterus and may be independent of the corpus luteum.

Summary

Functional uterine bleeding may occur when a corpus luteum is present in the ovary. The endometrium in some instances may evidence irregular regression (Specimens 335, 332, 334, 293, and 265). The irregular regression is the result of prolonged life and function of the corpus luteum. The endometrial picture will vary, depending upon the rate and extent of regression of the corpus luteum. The bleeding which occurs seems to be an exaggeration of the normal bleeding processes observed in cyclic menstruation.

The corpus luteum in other instances may be histologically and functionally normal. The endometrium, except in small regions, responds normally. It is from these small regions that bleeding occurs. The bleeding in these instances is independent of the corpus luteum and of the remainder of the endometrium. The bleeding is unlike the usual normal menstrual bleeding. It is localized bleeding from blood sinuses with scant loss of endometrial tissues. During this type of bleeding ovulation can occur, corpus luteum development can progress normally, and the endometrium not involved in the bleeding can develop normally. (Specimens 257, 266, 273.) The phenomena that occur that produce the bleeding in such instances are not known. The explanation may reside in a local bleeding factor in the endometrium or in the local abnormality of response of the endometrium.

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Discussion

DR. M. E. DAVIS, Chicago, Ill.—It is not an easy matter to seek out bleeding points on the wide expanse of an endometrial surface and subject them to careful study.

No one can find fault with the histologic data presented. They have been accumulated by one thoroughly trained in the histologic anatomy and pathologic changes of the reproductive organs. The facts which Dr. Brewer presented are thoroughly reliable.

The physiologic interpretation of these findings, however, leaves room for many questions and, at least, a difference of opinion. It is difficult to accept a thesis which would cast doubt on many facts which we have considered as settled.

The normal hormonal control of the endometrium has been fairly well established. The growth of the endometrium, the development of the vascular mechanism, and bleeding are all the result of estrogenic stimulation. Bleeding is initiated by a sudden drop in the estrogen level, or perhaps by a change in the metabolism of this substance. That this is due to the direct action on the spiral arteries with the production of ischemia and necrosis is not known. If estrogens play the dominant role in the mechanism of normal bleeding, what is the function of progesterone? It is entirely possible that this hormone is responsible for progestational changes only. Thus, the edema of the stroma, the development of the decidual cells, the secretory changes in the glands, all necessary to normal nidation, are the result of progesterone.

If this thesis is correct, there is little difference between ovulatory and anovulatory bleeding. In the normal ovulatory cycle estrogens are supplied in the preovulatory phase by the growing follicle and the postovulatory phase by the corpus luteum. In anovulatory bleeding the estrogenic stimulation may be prolonged and variable, thereby resulting in irregular bleeding patterns. It is not necessary to postulate the presence of a bleeding factor to explain some of the discrepancies in these case histories. Deranged hormonal controls could explain most of the findings.

The cause of local areas of endometrial necrosis may well represent underlying local vascular changes. It is possible that the estrogenic influence may not extend to the entire vascular bed or that some areas are less sensitive to stimulation. It is likewise possible that such areas may continue to bleed for long periods of time.

Lastly, there are few studies correlating the histologic appearance of corpora lutea and their endocrinal function. The appearance of a corpus luteum may not be an accurate index of the endocrinal influence it exerts on the target organs. Much more data will have to be accumulated before we can answer many of the provocative questions raised by the essayist.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Brewer's paper underlines the correctness of the statement so often made that bleeding can occur from any histologic type of endometrium. The type of endometrium with which his paper deals is certainly not to be compared in frequency with the anovulatory form of functional bleeding. The latter is due to an aberration of the anovulatory type of cycle, numerically much less common than the ovulatory, but occurring with especial frequency at those phases of menstrual life when functional bleeding is so often seen, i.e., puberty and adolescence on the one hand, and the premenopausal period on the other. This in itself is suggestive. The anovulatory cycle appears to be a more primitive, incomplete, and unstable one than the ovulatory.

Dr. Brewer's cases, however, appear to represent a subvariety of the ovulatory variety of bleeding, concerning whose mechanism we know very little. I do not believe that most

eases would show such areas as Dr. Brewer has shown in his slides, and in which the mechanism may involve some local factor in the endometrium as he himself suggests.

Since the spiral arteriolar system is so important in the production of normal menstrual bleeding, it has been suggested that a local vascular abnormality or disturbance may play a chief role in the production of the ovulatory type of bleeding. Dr. Reynolds has stated that spiral arterioles are completely absent in the endometrium of certain African monkeys which menstruate quite normally. There appears to be an innate bleeding propensity in the endometrium, this being histologically expressed in more elaborate form in the spiral arteriolar apparatus observed in most monkeys and all human females.

As to the local factor suggested by Dr. Brewer, I am more and more convinced that this must always be reckoned with in the interpretation of many endometrial lesions. Side by side, in the same endometrium, under the influence of the same hormonal factors, one may see an area of beautiful progestational appearance and one of Swiss-cheese hyperplasia, and other instances of localized variations in the sensitivity or refractoriness to the ovarian hormones might be cited.

DR. BREWER (Closing).—It seems to us that the endometrial responses have been neglected in the various manifestations and phenomena of uterine bleeding, and we feel that they are important. It is difficult to explain some of the bleeding phenomena on the basis of the endocrine function when the major portion of the endometrium has responded in a completely normal way. We feel that since these relationships are normal and the tissues are normal—and in the last specimens we had chemical analyses indicating that they were normal—the bleeding must be due to some other factor which is local in the endometrium. We do not believe all mechanisms are as yet explained.

ATYPICAL ENDOMETRIAL HYPERPLASIA SIMULATING ADENOCARCINOMA*

EMIL NOVAK, M.D., AND FELIX RUTLEDGE, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins Medical School)

THE purpose of this paper is to call attention to a group of benign hyperplastic lesions of the endometrium which may be and often have been mistaken for adenocarcinoma. While these lesions are actually hyperplastic in a general pathological sense, they are very different in their histologic characteristics from the ordinary type of benign endometrial hyperplasia. The latter term has come to have reference in gynecologic literature to the Swiss-cheese type of endometrium, characterized especially by disparity in the size of the glands, some being large and cystic, and some small, together with a rather abundant, compact stroma. The term, as first applied by Cullen, seemed appropriate for a lesion in which both epithelial and stromal elements exhibit hyperplasia. It does not apply to endometria which show only an occasional cystic gland, for this may be found in even a typical normal progestational endometrium, frequently in the basalis and not so infrequently in the functional layers.

For that matter, areas of Swiss-cheese endometrium of even considerable size may be found in otherwise normally functioning endometrium, representing what might be considered intraendometrial polyps made up of unripe endometrium similar in appearance to that making up most endometrial polyps growing from the surface. We mention these things simply to emphasize that the reaction of the endometrium to the ovarian hormones is not always the same in all its parts, just as its reaction is normally different at different endometrial levels.

The histologic appearance of any part of the endometrium is determined not only by the hormonal influence to which it is subjected, but also by its own degree of sensitivity or refractoriness to the hormones in question. The degree of maturity or immaturity, ripeness or unripeness of the endometrium, appears to be the most important factor in determining the degree of its receptivity to the ovarian hormones. In general it seems to be true that young, immature endometrium is highly responsive to the growth effect of estrogen and refractory to the differentiating hormone, progesterone. The reverse appears to be true of more mature endometrial elements, such as those normally found in the functionalis.

It is of interest that Schröder, who deserves the chief credit for the complete description of hyperplasia, as well as its cause and its relation to functional bleeding, selected exactly the same designation for this lesion as had Cullen

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many years earlier. At the outset, to avoid misconception of our paper, we would like to emphasize two points.

The histologic picture presented by the ordinary Swiss-cheese hyperplasia does not in the slightest degree resemble that of adenocarcinoma. Secondly, the ordinary hyperplasia as observed during reproductive life has no tendency toward malignant transformation. It is true that Meyer¹ has reported one or two instances of carcinoma occurring in association with such hyperplasia, but the rarity of observations, in a condition as common as hyperplasia, makes it seem certain that any association must be looked upon as coincidental. A number of authors (Novak and Yui,² Taylor³) believe that the endometrial hyperplasia not infrequently seen in women well beyond the menopause may play a predisposing role in the development of cancer, but we are not here concerned with this problem.



Fig. 1.—Patient, aged 49 years, had had x-ray induction of menopause four years previously. For some months before curettage the patient had taken 1 mg. stilbestrol daily for menopausal symptoms, followed by bleeding five days after withdrawal of drug. Picture shown above had been diagnosed adenocarcinoma, but was considered by us to be benign. Repetition of curettage four or five weeks later showed regression of endometrium to extreme senile atrophy (see Fig. 2).

We have been impressed with the fact that the simple type of Swiss-cheese hyperplasia does not represent the only abnormal endometrial pattern which may be produced by excessive or prolonged estrogen stimulation, either in the human female or in the experimental animal, and that these other growth patterns are often totally different in histological appearance from the Swiss-cheese type. The term hyperplasia, as used in gynecologic literature, has come to refer to the Swiss-cheese type, but the atypical forms are just as hyperplastic from a pathologic standpoint. This atypical hyperplasia may be fairly uniform throughout the endometrium, but more frequently the atypical lesion occurs in one or in many localized areas of an endometrium which otherwise presents an

obviously benign Swiss-cheese picture. Only two interpretations of these localized, cancerlike areas seem to offer themselves. One is that these often highly atypical areas actually represent multicentric carcinoma developing in benign Swiss-cheese hyperplasia. The other would be that these abnormal cancerlike areas represent different degrees or types of estrogen effect upon areas which respond differently to the same estrogen growth stimulus. This we believe to be the correct explanation, as we hope to show in this paper. This conclusion carries with it also the connotation that such areas are not histologically indicative of malignancy.

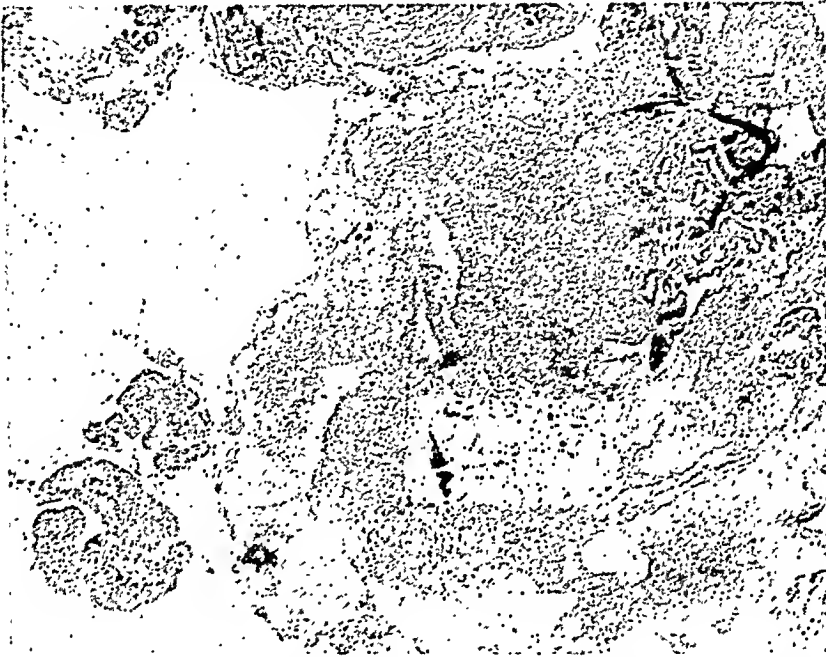


Fig. 2.—Extreme atrophy of endometrium, with no suggestion of carcinoma in same case as shown in Fig. 1. Only few fragments of senile endometrium obtained, picture showing chiefly blood.

A good illustration of the variations in the histologic effect produced by the same estrogenic agent is seen in the examination of the endometria of women who have been taking diethylstilbestrol, often in considerable dosage, continuously for inordinate lengths of time. No gynecologist need be told that the abuse of this drug, in itself a very valuable one, is a widespread evil, and that postmenopausal bleeding is a frequent result of such injudicious therapy of menopausal vasomotor symptoms. We have had the opportunity of examining a number of the endometria of such patients, and of noting that the hyperplastic effects of the drug vary greatly in degree and in character. While in some cases they are of mild degree and usually of benign Swiss-cheese character, in the occasional case they are very atypical, with such high degrees of adenomatous and proliferative activity that they may easily be mistaken for adenocarcinoma.

Fig. 1, for example, represents the endometrium of a postmenopausal woman who had been taking stilbestrol for many months and who developed postmenopausal bleeding which led the surgeon to do a diagnostic curettage. A di-

agnosis of adenocarcinoma was made by two competent general pathologists, and radical operation advised. The sections were sent to our laboratory for examination, and we interpreted them as benign. The suggestion was made that a repeat curettage be done in a month, the stilbestrol having of course already been discontinued. Fig. 2 shows that the endometrium had regressed to the normal postmenopausal pattern.



Fig. 3.—Very mild hyperplasia, not of typical Swiss-cheese type, and not at all suspicious of malignancy, in woman 55 years of age, treated with curettage and x-ray.

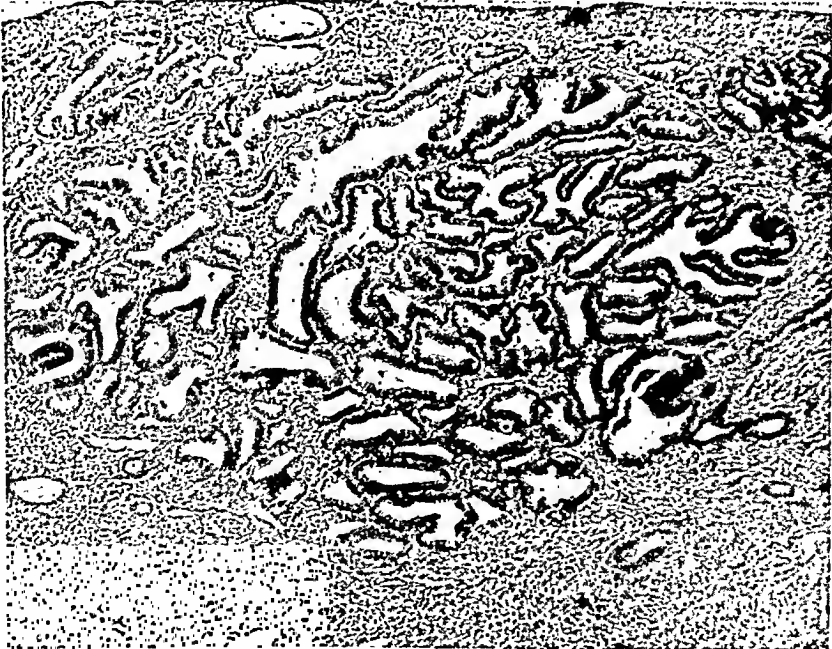


Fig. 4.—Adenomatous hyperplasia in woman 55 years of age, following previous excessive stilbestrol. This patient had a hysterectomy. Section is from near uterine cornu.

What are some of the atypical proliferative patterns which may lead to the incorrect diagnosis of carcinoma? They may be put down as follows: (1) increased number, crowding, and moderate atypicalness of the glands; (2) stratification, abnormal staining, and atypical morphology of the epithelium; and (3) the presence of squamous plaques in the walls of the glands, and occasionally on the surface.

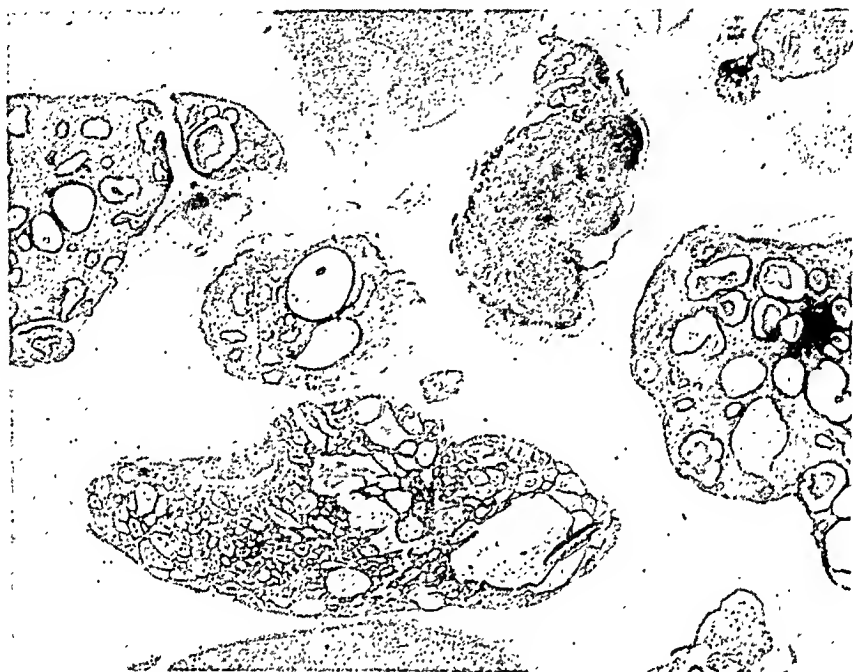


Fig. 5.—Adenomatous crowding of glands in small polyp in lower portion of picture, remainder of endometrium showing Swiss-cheese pattern. Patient was 62 years of age, and had had a postmenopausal hysterectomy.

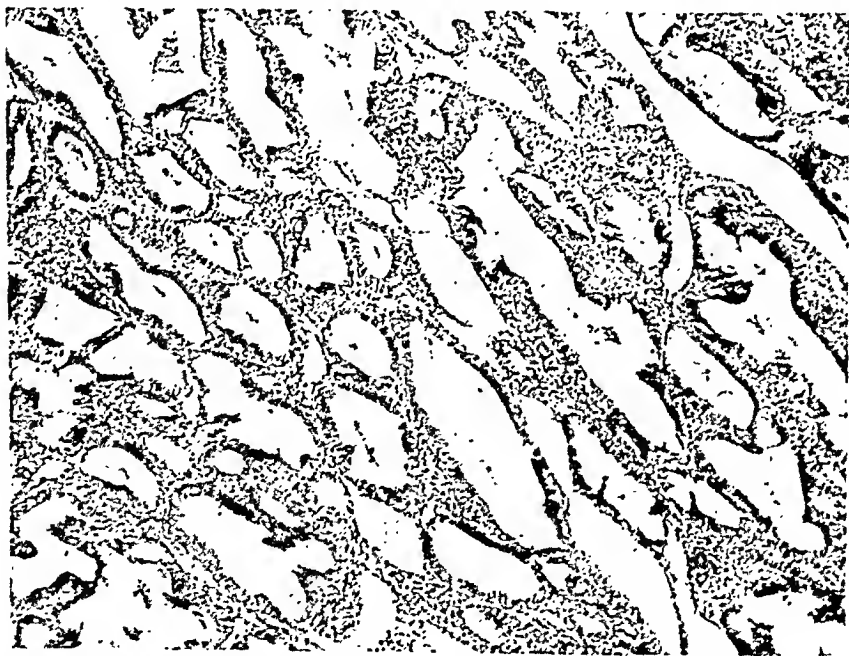


Fig. 6.—Markedly adenomatous picture in a woman 41 years of age, who had curettage followed by hysterectomy, without preliminary radiation. No gross lesion was found, and the patient was well two years later. We do not think this lesion was malignant.

1. In the ordinary Swiss-cheese type of endometrium the glands are scattered discretely in an abundant stroma. In the atypical forms of hyperplasia, the glands are greatly increased in number, with very little intervening stroma, and in such areas no cystic glands are likely to be seen. In some of these adenomatous areas the glands show comparatively little convolution, in others



Fig. 7.—Pseudomalignant hyperplasia in woman 49 years of age, who had only curettage and x-ray induction of menopause one year previously. No bleeding since then. Note tall, well-differentiated epithelium with small needlelike nuelei.



Fig. 8.—A relatively common finding in atypical hyperplasia is seen in the pale staining areas, often multiple, probably explained by the immaturity of the epithelium. This is not indicative of malignancy. The hysterectomy in this patient, aged 52 years, was probably unnecessary. There was no radiation. No gross lesion was found, and she is well one and one-half years after operation.

the gland pattern is as atypical as in many instances of adenocarcinoma. Marked adenoma-like crowding of the glands is especially common in endometrial polyps, which are usually made up of an immature type of endimetrium.

2. Even in clearly benign hyperplasia stratification of the gland epithelium is not uncommon, especially in the smaller noncystic glands. As a rule, however,

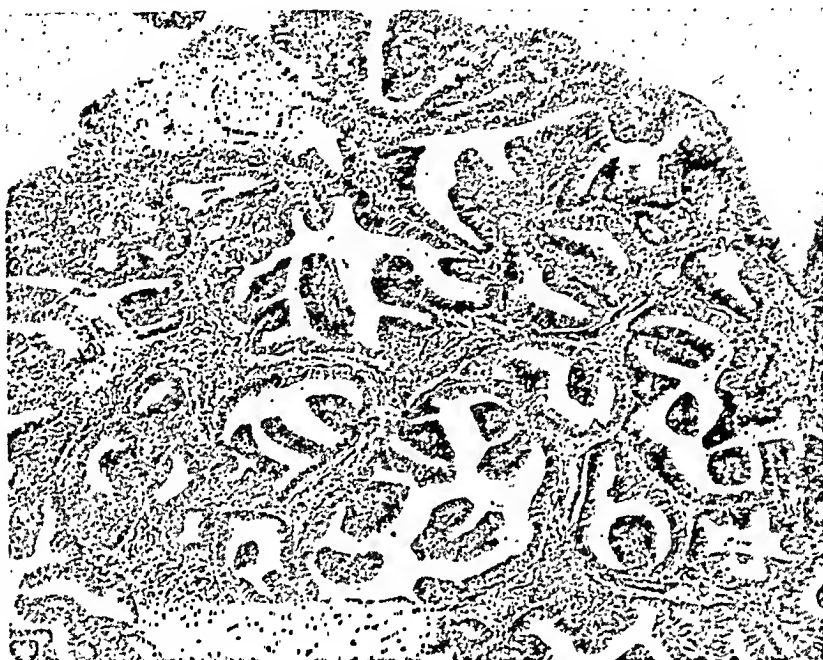


Fig. 9.—Patient aged 29 years had a hysterectomy without preliminary radiation. The removed uterus showed no lesion, and she is well two and one-half years after operation. While this lesion is certainly highly suspicious, and hysterectomy was justified, we are inclined to believe that the picture represents an atypical hyperplasia rather than adenocarcinoma.



Fig. 10.—This patient, aged 40 years, had curettage followed by hysterectomy, which showed no gross lesion, and she was well when last heard from, ten years later. Note the peculiar syncytial-like metaplasia on surface, and in one or two of the glands.

not more than two layers of cells are seen. In the atypical variety such stratification is much more common and often extensive. The epithelial cells in both the typical and atypical forms of hyperplasia often show moderately large and dark-staining nuclei, but exceptions are noted in many of the atypical cases, in that the epithelium may be very tall, with small fusiform, sometimes almost needlelike nuclei. They are very uniform, with no suggestion of the nuclear hyperactivity characteristic of cancer.



Fig. 11.—Extensive squamous metaplasia in an endometrium which otherwise shows a benign, Swiss cheese hyperplasia. Such lesions are often diagnosed as adenoacanthoma and treated as cancer. They are probably sufficiently suspicious to justify this plan, which was carried out in this patient. No preliminary radiation was used, and no gross lesion was found in the removed uterus. She was 35 years old, and was well nine years later.

Such areas often stand out very sharply from the surrounding endometrium because of their pale staining, which seems explainable only on the basis of the greater immaturity of the cells. Not all such light staining areas are lined by the type of epithelium above described. Some show epithelium which consists of two types of cells similar to those characterizing the tubal epithelium, even to the presence of cilia. Such areas are to be interpreted as instances of the segmental differentiation anomalies so often seen in the genital canal (proso-plasia or retroplasia), as described in a previous paper by one of the present authors.⁴ The occasional finding of typical endometrium in the tube is another instance of such differentiation anomalies. Finally, though rarely, the stratification of either the surface or gland epithelium in cases of atypical hyperplasia may assume a peculiar syncytium-like appearance, as described in the paper by Novak and Yui in 1936.²

3. Squamous plaques may be noted in either benign hyperplasia of the endometrium or in association with adenocarcinoma (adenoacanthoma), the latter more frequently than the former. Many cases of adenocarcinoma have thus been wrongly interpreted as combined squamous cell and adenocarcinoma, but

the squamous plaques in themselves show no histological evidence of malignancy. A number of studies of these squamous nodules have been made (Polano, Sitzenfrey, Meyer, Engelhorn) and the prevailing viewpoint is that they have their origin from certain indifferent cell elements beneath the columnar cells. These indifferent cells possess differentiating potentialities which may result in the formation of small squamous nodules which at times push into the gland lumen in a glomerular-like fashion, as Meyer pointed out.⁵ The overlying gland epithelium may be displaced, while in other cases the squamous growth pushes out into the surrounding stroma, producing plaques of considerable size.



Fig. 12.—Extreme squamous metaplasia, with rather proliferative hyperplasia in a few areas of an endometrium which in most parts was of Swiss-cheese type. The patient, aged 55 years, not postmenopausal, was curetted, with no radiation or hysterectomy. No symptoms two years later.

When such squamous areas occur in a benign hyperplastic endometrium, as they occasionally do, they bring about a picture which is apt to appear more wicked histologically than it is clinically. At any rate, they are not in themselves to be looked upon as evidence of malignancy. It is on the characteristics of the gland elements that one should base such a diagnosis. It is our belief that a diagnosis of adenoacanthoma is not infrequently made in cases of benign hyperplasia associated with such squamous cell islands.

All the changes described above were described in papers by Hintze⁶ and Meyer,¹ both emanating from Meyer's laboratory. In all of the twenty-four cases reported by Hintze, there was no other treatment than curettage, and a follow-up of these cases revealed no evidence of subsequent carcinoma in any of them. A similar small group were described by Novak and Yui in 1936, and in a very recent paper by Corseaden and Gusberg,⁷ a number of illustrations portray lesions of this general character, the authors interpreting most of them as atypical carcinomalike hyperplasia rather than actually malignant. A study

of these photomicrographs leads us to believe that they are correct in making such an interpretation. This about exhausts the literature of the subject, so far as we can learn, in so far as human observations are concerned.

In the realm of experimental studies of estrogen stimulation upon the lower animal, there is a large amount of evidence to indicate that all gradations of abnormal growth effect may be produced in the endometrium, with often just such atypical hyperplastic and canceroid changes as we have been discussing. The most recent and most provocative study of this sort is that made in 1944 by Crossen and Loeb,⁸ who describe stratification of the epithelium, squamous metaplasia, and papillary changes in both the surface and gland epithelium. The lesions illustrated in their paper are quite like those which we have pictured in this paper, though no actually cancerous lesions were produced. They draw the same conclusions which have been impressed upon us as to the individual nature and degree of the responsiveness of endometrial tissue to estrogenic stimulation.

Material for Study

The material forming the immediate basis for this study consists of a group of cases which show atypical hyperplastic changes which might readily be mistaken for adenocarcinoma, and which, as a matter of fact, were actually so diagnosed in many instances. These cases were selected from a considerably larger group exhibiting less pronounced atypical pictures which few would interpret as malignant. The question naturally arises as to the criteria on which we have decided that the lesions in question are not actually malignant. These will be apparent from the grouping which we have adopted for the cases with these histologically questionable characteristics.

Group I. Cases receiving no treatment except curettage, or curettage plus radiologic induction of the menopause.—

If a woman is submitted to diagnostic curettage for uterine bleeding, we feel it entirely safe to assume in retrospect that the endometrial lesion was benign if she remains perfectly well for a term of years with no further treatment, or with no other treatment than x-ray or radium induction of the menopause, in a dosage which no one would consider adequate for the cure of carcinoma.

In this group we place eighteen of our cases, all showing histologic changes, sometimes diffuse and sometimes localized, which might easily have been mistaken for carcinoma. Sometimes the pseudomalignant picture occurred only in a single area, sometimes such confusing areas were multiple.

Eight of these eighteen cases had curettage alone, with no subsequent radiotherapy, and no further operative procedure. One of these is of special interest because the bleeding followed excessive diethylstilbestrol therapy in a woman 49 years of age, who four years previously had had x-ray induction of the menopause. This case has already been alluded to, and is illustrated in Figs. 1 and 2. The ages of the other patients in this group were 18, 21, 30, 33, 44, 49, 53, and 55 years. Only the one patient mentioned above was postmenopausal. This age distribution in itself is very different from that of adenocarcinoma, and this point we shall discuss later in this paper.

All eight of these patients have remained well for periods of from 1 to 21 years after the curettage. The 21-year-old patient in this series was delivered of twins sixteen years after the curettage. Another one of these patients is of special interest in that she remained well for fifteen years following simple

eurettage, but then returned to this hospital with an adenocarcinoma which was treated by hysterectomy, preceded by radiation. This case perhaps is illustrative of the view, supported by the statistical studies of Corsecaden and Gusberg,⁷ and Randall,⁹ that patients who have had menopausal functional bleeding have three and one-half times as great a chance as other women developing adenocarcinoma in later life.

As will be noted, even comparatively young patients may at times reveal these histologically disturbing pictures, as strikingly shown in one of the cases of this group. Because of excessive bleeding, this patient was curetted at the age of 18 years. A diagnosis of adenocarcinoma was made, and this was confirmed by one of the leading pathologists of the country. She was referred to one of us (E. N.) for further management. It was our opinion that the slide (Fig. 13) represented an atypical but benign hyperplasia. There had been no further abnormal bleeding, and no further treatment, organotherapeutic or otherwise, was considered necessary. The patient was later married and experienced a normal full-term delivery. In 1943 she was operated upon for the removal of a large dermoid cyst of the left ovary. In 1946 she was referred back to us because of a tumor, about the size of an orange, in the remaining ovary, and another large dermoid was removed, together with the uterus. The endometrium was entirely normal. Figs. 3 and 7 are further good examples of the atypical hyperplastic pictures encountered in this group of cases.



Fig. 13.—Endometrium of a girl 18 years of age, with moderate proliferative activity, but diagnosed as Grade I adenocarcinoma by a leading pathologist. No treatment after curettage, and patient well many years later.

The remaining ten cases of this very conservatively treated group received sterilization doses of either x-ray or radium. We have not been able to secure a follow-up of two of the older patients in this group, but the remainder have remained well, with no evidence of subsequent adenocarcinoma. These patients varied in age from 30 to 57 years.

Group II. Atypical hyperplasia, with subsequent hysterectomy, without preliminary radiation.—

In the ordinary case of adenocarcinoma, even after preliminary curettage, one expects, if the patient has not had preoperative radium, to find some gross

evidence of the cancer lesion when the removed uterus is opened. We appreciate that there are exceptions to this rule, as in the case of very small lesions, usually polypoid, which might have been entirely removed with the curette. Such cases, however, are relatively rare. Moreover, of the twenty-six cases which we have placed in this second group, all but one showed extensive areas in the endometrium of the removed uterus quite similar to the atypical lesions in the curettings. And yet, with one exception, there was no suggestion of a gross lesion. In view of the widespread microscopic changes, the absence of any gross lesion seems to us almost incompatible with the diagnosis of malignancy. In only one case was there a "small projection" on the endometrium, but this showed no microscopic suggestions of adenocarcinoma.

The atypical hyperplastic changes seen in this group of cases were often of a much more pronounced grade than those noted in our first group, and the simulation of cancer therefore much more perfect than in the latter. In many of these cases there was a difference of opinion among the pathologists of our group as to whether or not these lesions should be diagnosed as adenocarcinoma.



Fig. 14.—Endometrium of a woman 47 years of age, who had hysterectomy without preliminary radiation following the curetting. No gross lesion, and patient was well three and one-half years later. It was in this case that Josef Halban made the comment quoted in the text, "Nicht Karzinom, aber besser heraus!"

It is of interest to note that it was an examination of the sections from one of these cases (Fig. 14) that inspired the late Josef Halban on a visit to our laboratory to make the comment which we have so often quoted, "Nicht Karzinom, aber besser heraus!" This, as a matter of fact, has been our policy in this group of cases, and we believe it to be the safe one, even though such a retrospective study as this makes us feel that in these lesions the decisive cancer change had not occurred, and that these patients would probably have been cured by radiotherapeutic induction of the menopause.

The ages of these twenty-six patients varied from 29 to 66 years, distributed as follows: 29 years, 2; 35 years, 2; 37 years, 38 years; 39 years; 40 years; 41 years, 2; 43 years; 47 years; 48 years, 2; 49 years, 2; 52 years, 2; 56 years; 59 years; 62 years; and 66 years. In four patients having their source in outside clinics, the ages could not be accurately ascertained. It may be noted that

only three of these patients had passed the menopause. One of these, aged 59 years, had ceased menstruating five years previously, and in her case, the bleeding and the hyperplasia were obviously the result of injudicious stilbestrol therapy. One patient 62 years of age had had her menopause twenty years previously, and one 66 years of age, ten years before. It thus seems that postmenopausal hyperplasia may at times assume an atypical form, but that the great majority of such lesions are encountered while the ovaries are still functioning, and probably overfunctioning in the sense of producing a relative estrogen excess. This fact should make us suspect that the endometrial lesion is an estrogen-induced growth effect rather than a neoplasm.

Equally suggestive is the fact that only three of the twenty-six cases were postmenopausal. Such an age incidence is totally different from that of adenocarcinoma, which in approximately three-fourths of cases is a postmenopausal disease.

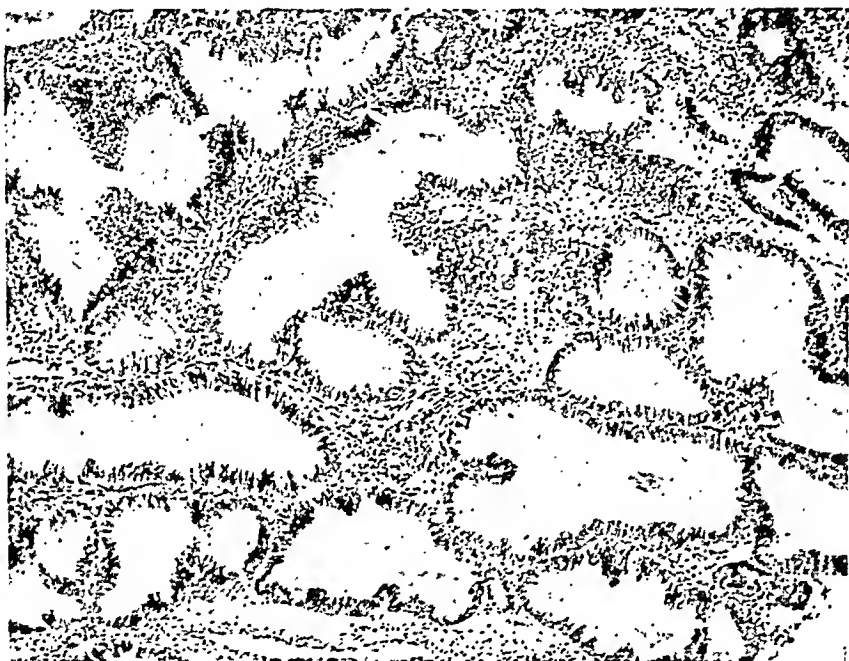


Fig. 15.—Another field in the endometrium shown in Fig. 13.

A follow-up of these cases was possible in all except six, most of which came from outside clinics. With three exceptions, all the cases date back more than three years, and every one of the twenty cases has remained well for periods varying from one to many years. It would be difficult to believe that such results could be achieved with actual carcinoma.

In some respects this group of endometrial lesions seems comparable to the so-called preinvasive carcinoma of the cervix, which likewise is clinically benign in the genuinely preinvasive phase. In at least some of our cases, the pseudomalignant change affected only the basal layer, while the overlying more superficial endometrium was fairly normal. Even where the changes were more diffuse, they were more pronounced in the basal layer, suggesting an abnormally exaggerated growth effect rather than a neoplasm. Moreover, there was an absence of the necrosis one would expect to find in carcinoma of corresponding extensiveness.

There was in no case any evidence of invasiveness, in the sense of penetration of the basement membrane or of myometrial involvement. It is true that it

is not always as easy to demonstrate invasiveness in undoubted adenocarcinoma of the endometrium as in the epidermoid carcinomas of the cervix, even though one may feel sure, from the occurrence of the metastases and other malignant characteristics, that invasive penetration into the lymphatics unquestionably occurs.

This leaves for final consideration the study of individual cell changes as a possible aid in the separation of benign and malignant lesions which, in so far as general architecture are concerned, seem to show no very striking differences.

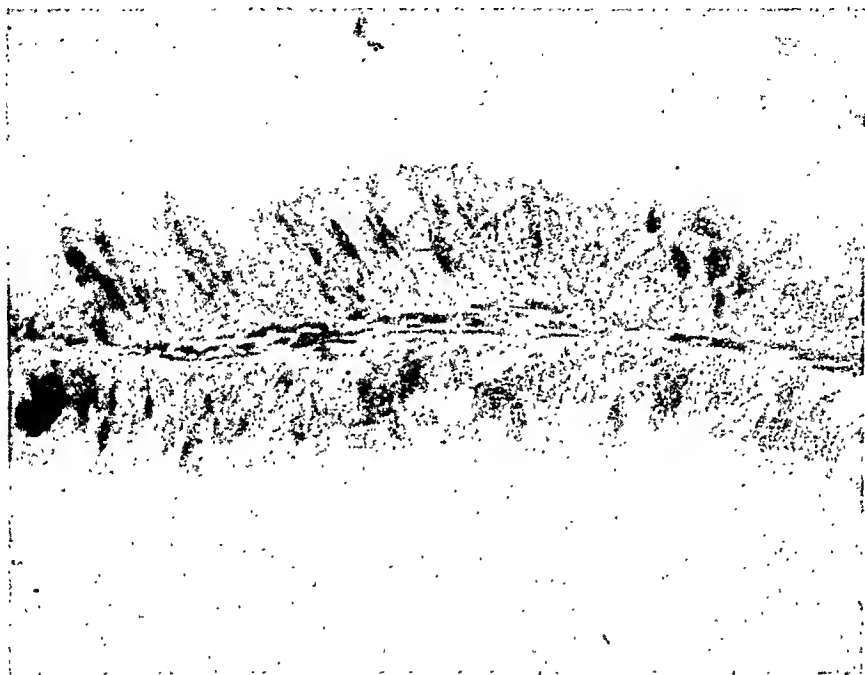


Fig. 16.—High power of the epithelium in two adjoining glands of case shown in Figs. 13 and 14. The epithelium is tall, pseudostratified, and the nuclei are comparatively small, long, and narrow, with no evidence of undue activity.

In at least some cases, the character of the individual cells would seem to be a reliable criterion, but in others it may be precarious. In some of the atypical hyperplastic cases the epithelium may show striking stratification, but the cells are tall, very narrow, with long, almost needlelike nuclei, with no sign of overactivity, and quite small in relation to the cell as a whole. In others the epithelium, as has already been mentioned, shows no stratification, no nuclear overactivity, and may resemble tubal epithelium. However, even in very benign hyperplasia of the Swiss-cheese type, the nuclei are at least moderately large and stain rather heavily with hematoxylin. Mitoses are of little differential value, since they are just as likely to be seen in benign hyperplasia as in adenocarcinoma.

While such cell study is thus of value in certain cases, it will leave the pathologist still uncertain in others, and we repeat that in the present state of our knowledge these genuinely doubtful cases should be treated as carcinoma.

In addition to the two groups described above, we have studied a third which we do not wish to submit as evidence to support our thesis, but which has revealed at least suggestive information along this line. During recent years, irradiation has preceded hysterectomy for adenocarcinoma in our clinic, as in most others. On re-examining the original curettings on which the diagnosis was made, we have encountered twelve patients in which the lesion is of the borderline group we have been discussing. In none of these was there any evi-

dence of carcinoma, either gross or microscopic, in the uterus after its removal. Our experience, like that of most others, has been that residual carcinoma can be expected in something like 50 per cent of carcinoma after presumably adequate intra-cavitary radiation. Either the radium in these cases was extraordinarily effective, or at least some of these were not malignant. In at least seven of the cases a review of the original sections shows lesions which we feel sure are benign, as in our Group 1 cases. In the other five they are of such suspicious type, like our Group 2 cases, that certainly the radical treatment employed was fully justified.

Discussion

In the study of any very large number of hyperplastic endometria one will encounter every possible histologic gradation between the frankly benign and the obviously malignant. In the majority of cases of adenocarcinoma of the endometrium the malignancy arises in a normal, nonhyperplastic endometrium, and the contrast between the benign and the malignant area is usually clear enough. But the atypical hyperplastic endometria being discussed in this paper may present difficulties of diagnosis.

The fact that the histologic transition between the benign and the malignant lesions is marked by almost insensible transitions does not of course mean that these gradations indicate the gradual transformation of a benign to a malignant lesion. The important consideration is that the irreversible somatic mutation which transforms a normal epithelial cell into a cancer cell is probably of short duration, and in the beginning cannot as a rule be determined by any histological method now available.

Comparatively soon it may engender certain cruder characteristics, such as obvious epithelial dedifferentiation, nuclear changes or even invasiveness, which make the distinction easy. But other common microscopic characteristics of adenocarcinoma are no less marked, and sometimes more so, in certain of these atypical hyperplastic processes than in the actually malignant one. It is another way of reiterating what most pathologists have always emphasized, that a lesion either is or is not a cancer, but that in individual cases it is simply impossible to make the decision by microscopic examination.

After all, the decision as to whether or not a given lesion is malignant or benign could best be made by the patient herself, were we to let her unfold her own story to recovery or to ultimate death. But we cannot use the human patient as a laboratory experimental animal. We must therefore do our best to separate these atypical lesions into two groups: (1) one in which, in spite of certain atypical characteristics, we can be quite certain that cure can be effected by simple conservative treatment, thus avoiding extensive surgery, which is not without hazard, and also imposes on the patient the cloud of future uncertainty which is the inevitable lot of every cancer patient; (2) the group in which the possibility of already existing cancer cannot be eliminated, and in which conservative treatment might dangerously delay adequate cancer therapy.

We are convinced that every case in our Group 1 was nonmalignant, and we would not hesitate to employ conservative methods in the type of endometrial lesions found in this group. We are unorthodox enough to feel that all or nearly all of the lesions described in our Group 2 patients were also not malignant,

and yet we are convinced that such pictures are very often interpreted as adenocarcinoma. As a matter of fact there are few of us who would have the courage to withhold radical treatment in such cases. In these genuinely uncertain cases we ourselves practice this plan, although the time will probably come when we shall have available some more precise means of sifting out the benign lesions from those in which the irrevocable cancer mutation has occurred.

The fact that forty-four instances of these questionable lesions have been revealed by a survey of our own material which is not by any means exhaustive leads us to believe that in the aggregate they are numerous enough to have some vitiating influence on cancer statistics. Mistakes in pathologic diagnosis are of course inevitable in all fields of pathology, but we believe that in the endometrium, as in the breast, such misinterpretations are disproportionately common because these organs are under the physiological influence of estrogen. The ability of estrogen to produce pseudoneoplastic lesions in both the uterus and the breast has been abundantly established by experimental studies, and we believe that the lesions we have described in this paper belong to this category.

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Discussion

DR. WILLARD COOKE, Galveston, Texas.—Dr. Novak's paper indicates very clearly the necessity for the development not only of specially trained gynecologic pathologists, but of pathologically skilled clinicians. Under ideal conditions the material removed in the operating room should pass immediately to the laboratories of the clinical department in order that significant tissues may be selected in the light of clinical knowledge and curiosity, and may be blocked and cut in the most effective directions. This is, of course, impossible in the case of the private practitioner and, unfortunately, in many schools. It is, however, quite possible, at almost no cost, to have duplicate slides made by the pathologist for immediate study by the clinician—a procedure which should be universal.

In regard to the subject of Dr. Novak's paper, there are two points which require consideration. We may accept as a fact that the endometrial response to the cyclic hormonal stimuli is not always uniform either in degree or in timing. The assumption, however, that atypical localized changes in the endometrium are due to variations in hormonal supply, particularly if we restrict to a single hormone, must in our present state of ignorance in regard to the actions of these hormones, remain an assumption only. The fact that all of Dr. Novak's cases occurred in sexually active patients except for the single postmenopausal patient under artificial estrogenic therapy is suggestive. Yet, while I had not time for a review of our material, I have the definite impression that we have encountered lesions of the types described in uteri removed (for prolapse, etc.) from elderly, asymptomatic patients. Many years ago, upon encountering such lesions, I classified them as subsurface, sessile, or pedunculated adenomas. While we all recognize the grossly proliferative varieties of endometrial hyperplasia, I find it difficult to conceive of a single, massive definitely pedunculated papillary growth with a typical stroma and vascular distribution—occurring in the midst of an endo-

metrium either totally atrophic or undergoing perfectly normal cyclic changes without evidence of hyperplasia—as the result of a localized selective estrogenic effect. Similarly, I find it easier to conceive of histologically identical glandular formations as adenomata of independent unknown origin. This is particularly true if such lesions occur in otherwise clinically and histologically normal endometria—a condition which is not very rare.

The only rational basis for the selection of treatment in any case lies in the knowledge of the comparative ultimate risk to the patient of the various possible therapeutic measures: in the present instance, curettage plus observation, radiation, hysterectomy. We have a fairly clear idea of the risks attached to each of these three procedures per se. If further extensive study of these lesions determines their potential for immediate or remote malignancy, our rationalism will be greatly advanced. For the present, however, eradication is indicated when definite uncertainty exists.

DR. GEORGE GARDNER, Chicago, Ill.—Once more Dr. Novak, in collaboration with Dr. Rutledge, has selected a topic for his presentation which is vitally interesting. In support of his thesis he has cited forty-four pertinent cases from the files of the Johns Hopkins Laboratory of Gynecologic Pathology. But, so far as I can ascertain, their division into two groups is based essentially on the treatment given. The first group was subjected to curettage with or without radiation castration; in the second, the uterus was removed and radiation was not employed. Are you not impressed that the method of treatment is an unusual criterion for separating atypical hyperplasias into those that are benign with certainty, and those which are probably benign? Dr. Novak, we regret, has failed to describe the details of histologic differences between these two groups of endometria.

The term hyperplasia denotes an increase in the bulk of a structure, due to an increase in the number of its component parts. Consequently, in the endometrium there is a *physiologic hyperplasia* which occurs during the proliferative phase of each normal menstrual cycle. Although all of us are conversant with the classical picture of full-blown pathologic hyperplasia of the endometrium, where there is an abnormal proliferation and increase in both stromal and gland elements, each of us has great difficulty, in fact finds it practically impossible to define those features which determine the exact transition from physiologic to pathologic hyperplasia. Furthermore, we recognize that the gland and stromal elements do not always respond equally to the growth impulse; as a result many endometria evidencing pathologic hyperplasia reveal the atypical glandular features which Dr. Novak has again brought to our attention, i.e., instances where gland elements have proliferated more actively than stroma cells and reveal (1) increased number, crowding, and moderate atypicalness of the glands; (2) stratification, abnormal staining, and atypical morphology of the epithelium; and (3) the presence of squamous plaques in the walls of the glands, and occasionally on the surface. I hasten to add that the more prompt the fixation of tissues in a proper fixative, such as Bouin's fluid, and the more skilled the preparation of slides, the more frequently is one likely to see these atypical features in endometrial glands.

On the other hand, we are surprised that Dr. Novak did not comment on specimens in which there was an unusual response by stroma cells, because in some atypical hyperplasias they may manifest predecidual changes. Neither did he comment on the effect of infection per se on the pattern and appearance of endometrial glands, although in one of his slides there is marked leucocytic infiltration. Also we question his statement that a tubal type of epithelium in the endometrium is an abnormality; some authorities, Bartelmez for example, recognize the presence of ciliated cells interspersed among "secretory" cells in practically all normal endometria.

Finally, we come to the crux of the problem. Is it possible, with a high degree of accuracy, to differentiate histologically between atypical glandular hyperplasia and early adenocarcinoma of the endometrium? Each of us is constantly being confronted with this problem and all of us are confused; fortunately for the patients we have misdiagnosed many more benign cases as cancer, than cancers as benign hyperplasias. But we still have our problem with us because this charming presentation by Dr. Novak has in no way defined the criteria for accurately cataloging all questionable endometria. We must continue, as

we have in the past, believing that certain ones are benign, fearing that others are malignant and treating each one according to the dictates of our changing knowledge. Apparently we must wait a while longer for an elucidation of those features which make for certainty in the diagnosis of these atypical cases, because Dr. Novak has not yet given us the answer.

DR. SUBODH MITRA, Calcutta, India.—I would like to know whether it is possible to find out more about the preinvasive phase of adenocarcinoma of the body of the uterus similar to the condition Dr. Novak has found in the endocervix; and whether the second slide which he showed, and some of the later ones, come under this phase of cancer of the body?

DR. NOVAK (Closing).—To enlighten Dr. Gardner as to the method of selecting our material, I may say that the point of departure was the study of a large number of slides of cases which had been diagnosed as hyperplasia or adenocarcinoma, but in which we knew nothing as to the clinical histories. When we sifted out the cases we were gratified to find that those in which the slides showed lesions which we thought to be benign fell into the groups described in our paper, in which the clinical evidence was either convincing or highly probable that they were in truth benign.

I do not think that any pathologist would invoke the factors of defective fixation or infection in the explanation of such lesions as we have shown in these slides. The pictures which one sees with defective fixation are totally different and usually easily recognizable, while the lesions of chronic endometritis due to infection are dominantly interstitial, with usually little or no epithelial change, even with intense chronic inflammation.

Finally, as to the advantages of studying cases of this general type, these appear to us fairly clear. With many of the milder forms of atypical hyperplasia, there should be no hesitation in excluding adenocarcinoma. With the more pronounced cases, in which even a skilled gynecologic pathologist cannot be sure, the study of a large number of cases, perhaps in many laboratories, may show that all remain well and that they reveal no gross lesion in the uterus. If these findings could be established in a very large number of cases, the evidence would seem clear that they are not malignant, but that they represent an exaggerated local growth effect of estrogen, as we believe them to be. And yet nothing is more certain than the fact that innumerable cases of this sort have been and are being diagnosed as adenocarcinoma in the laboratories of this country.

At the Section meeting in Atlantic City last week, the distinguished foreign guest, Dr. Julius Heyman, of Stockholm, stated that in something over 800 cases of adenocarcinoma treated in the Radiumhemmet, fifty-five were considered doubtful by the pathologists, but were treated as cancer. Would it not be a real gain to cut down this large doubtful group by a little more intensive study than these doubtful cases have thus far received?

THE USE OF MULTIPLE SOURCES OF RADIUM WITHIN THE UTERUS IN THE TREATMENT OF ENDOMETRIAL CANCER*

A. N. ARNESON, M.D., WILLIAM W. STANBRO, M.D., AND
JAMES F. NOLAN, M.D., ST. LOUIS, MO.

(From the Edward Mallinckrodt Institute of Radiology; and the Department of Obstetrics and Gynecology, Washington University, School of Medicine; and the Barnard Free Skin and Cancer Hospital)

PROGNOSIS in cancer depends largely upon the stage of clinical advance. The degree of involvement cannot be estimated accurately, however, by either duration of symptoms or size of the primary lesion. Wide variations in clinical behavior occur in different individuals despite origin of cancer in the same type of tissue or organ. The onset of symptoms may be delayed until considerable advance in tumor growth has occurred. Other patients present operable lesions in spite of clinical symptoms present for relatively long periods. Small tumors may undergo prompt dispersion to regional and distance lymph nodes. With delay in spread, large bulky cancers of doubtful localization may be completely within an operable stage.

Differences in clinical behavior are due to variations in biologic properties of tumor growth. The effect of those properties on end results may be more complex, however, than is indicated on the basis of dispersion alone. Their effect upon prognosis may be greater among patients treated by irradiation. Interactions between cancer cells and normal tissues of the host result in variation in life span for different tumors of comparable clinical extent. Those values are reflected in clinical statistics, and until there is greater knowledge of biologic factors of tumor growth, it will be difficult to evaluate different methods of treatment on the basis of survival rates alone.

Among biologic factors believed to affect prognosis in endometrial cancer is the relationship between histologic type and end results. Better survival rates are shown for well differentiated tumors. One might expect undifferentiated forms to be more sensitive to radiation. It should be noted, however, that favorable radiosensitivity is not synonymous with curability.

Healy and Cutler¹ found radiation more apt to destroy differentiated types. Healy and Brown,² Bowing and Iricke,³ and others believe histologic typing to be of less prognostic significance for treatment by radiation alone. Miller⁴ was unable to find in histologic appearance a basis for selecting a suitable method of treatment. There is, therefore, variation in interpretation of the importance of histopathology in estimating prognosis, but the relationship to survival rates is well established.

Size of the uterus is also believed to affect prognosis. Healy and Brown² found better results among patients with uteri of normal dimensions. Uterine

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size forms the basis for clinical classifications used by Miller and Henderson,⁵ Crossen⁶ and others. With enlargement there is apt to be distortion of the intrauterine cavity. Many years ago Sampson⁷ noted the technical problems involved in radium treatment of such lesions.

Cancer of the corpus tends to remain within limits of the myometrium for long periods after onset of the tumor. For that reason a high percentage of patients are "clinically" or "technically operable" at the time diagnosis is established. In spite of considerable variation in survival rates reported for surgery alone, several authors^{5, 8, 9, 10} have shown on the basis of collected statistics that the average result from hysterectomy is on the order of 60 per cent. That value indicates that about 40 per cent of all "clinically operable" patients have extensions outside the volume of tissue removed surgically. It is interesting to note that operable stages of cervical cancer show about the same incidence of lymph node involvement. Corseaden⁸ states that many recurrences in cancer of the body of the uterus are at or adjacent to the vaginal wound and in the abdominal scar. The intimate relationship between uterine and vaginal lymphatics may be a factor in local reappearance, as vaginal metastases are not uncommon for endometrial lesions. Additional data on lymphatic dispersion may also reveal that corporeal cancer is disseminated more often than cervical carcinoma through ovarian lymphatics with connections to the more distant and secondary barrier of nodes along the aortic chain. In the attempt to lessen treatment failure due to dispersion as well as to contamination of the abdominal wound at laparotomy, a great many authors have advocated the use of preoperative irradiation. Miller and Henderson⁵ have preferred the use of x-rays. Others have employed only radium, and some have used both methods in conjunction with hysterectomy. All have reported some improvement in clinical results, but the degree of advance is variable for different series. Corseaden⁸ believes that average results for the combined treatment may approach five-year survival rates on the order of 80 per cent. Seheffey, Thudium, Farrell, and Hahn¹¹ emphasize the importance of a planned technique, and the reporting of results on the basis of treatment employed.

The use of preoperative irradiation has resulted in another index for evaluating the end result to be expected. Among 119 hysterectomies done after the application of about 3,600 mg./hr. of radium, Taylor and Becker⁹ reported persistence of tumor in 49.6 per cent. In that group the absolute five-year survival rate was 44.1 per cent. Among those in whom no tumor was identified the value was 73.8 per cent. Destruction of cancer within the uterus is obviously an accurate indicator of the biologic response attained by irradiation. In responses of that order it is reasonable to believe that favorable changes were obtained in tumor cells located at more distant points.

Stowe¹² has pointed out that thoroughness of search for residual cancer is not often specified and that many authors have failed to correlate observations with the amount of radiation applied. By careful review of gross specimens previously examined by routine laboratory study, persistent tumor was found in a few specimens reported as negative. The increase was on the order of 10 per cent. Tumor destruction occurs more frequently among well-differentiated types in uteri of small size. Persistence is often found at points of invasion into the uterine wall. Rarely have more than 50 per cent of specimens in a given series been free of tumor at the time of hysterectomy. Special apparatus, such as hysterostats, etc., have been devised in the attempt to treat more adequately patients with endometrial cancer. By use of those techniques a greater incidence of tumor destruction is to be expected. Variations noted for radium treatment have been due in part to the adverse effect of uterine enlargement and distortion of the cavity.

Heyman and Benner¹³ have developed one of the most efficient methods for applying radium within the uterus. Multiple tubes containing small quantities of radium are placed individually into the uterine cavity until all available space is filled. The contribution in dose from each source is small. By that means the risk of focal necrosis is lessened. In cavities of larger size the number of tubes employed is greater, thereby increasing the total amount of radium. The distribution of sources is essentially independent of distortion in shape or increase in space within the uterine cavity. From 1914 to 1933 a total of 354 patients were irradiated by means of a single linear source containing between 35 and 45 mg. radium. For that group the five-year survival rate was 45 per cent. Between 1934 and 1939 a total of 316 patients were irradiated by packing the uterus with weaker tubes of equal size and shape in sufficient number to fill the uterine cavity. For that group the five-year survival rate was 65 per cent. Heyman obtained by that method in all patients with corpus cancer a result equal to the average survival shown in collected statistics for hysterectomy alone in operable patients.

In the attempt to simulate the technique devised by Heyman, the method of radium treatment used at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital was modified in 1938. Prior to that time intrauterine treatment had been given by means of tandems containing from two to three tubes in linear arrangement. That applicator did not always meet the standard requirement of active length extending from the level of the external os to the top of the fundus. The first modification consisted in the use of small strips of gauze to hold in position multiple tubes of radium packed into the uterine cavity.¹⁴ The gauze was also intended to provide some distance between the stronger sources and immediately adjacent tissues. The method was not satisfactory. Many technical difficulties were eliminated by a special instrument developed in 1940.¹⁵ By means of an introducer the number of tubes placed within the uterus was increased considerably. Brass capsules of a standard external diameter were obtained for radium sources available at the institutions in question. Length of capsules varied according to length of the radium tubes, but in each instance the strength per centimeter active length was on the order of 5 or 6 mg. of radium. From ten to twelve such capsules can be packed into a uterine cavity of normal size. Capsules of greater external diameter are used in the cervical canal to maintain patency adequate for removal of the intrauterine radium. Stronger sources are used in the cervical capsules because there are no closely related tubes contributing materially to the dose falling at that region. More recently the use of intravaginal radium has been added to the procedure. Applicators are cut from sponge rubber to fit the vaginal vault. Radium sources are then buried in the rubber at suitable points. Patients receive a course of external irradiation with x-rays before the application of radium. Four pelvic fields are selected for treatment and approximately 400 roentgens (air) applied each day. Total doses to each area are on the order of 1,200 to 1,600 roentgens. Other physical factors are: 200 KV., 0.5 mm. en. filter, 50 cm. target-skin distance, and skin fields measuring 10 cm. by 15 centimeters. The beams are angled medially a few degrees for directing the radiation toward the center of the pelvis.

Between 1936 and 1941, inclusive, a total of ninety-three patients with endometrial cancer were treated on the ward and teaching services of the two institutions. In the earlier years of that period radium treatment was given by means of intrauterine tandems. During that period there was transition to the use of multiple capsules and routine application of x-rays and radium before hysterectomy. A few selected patients were treated by surgery alone.

The five-year end results are given in Table I. Patients treated by radiation alone were considered inoperable due to advanced cancer, or to constitutional disorders that increased the risk of surgery. That group represents approximately 45 per cent of the entire series with an absolute five-year survival rate of 27 per cent. There has been no division into "technically operable" and "inoperable" groups because the number of patients is small. Surgery was employed in 55 per cent of the series. Among those treated preoperatively with x-rays and radium there is a survival rate of 68 per cent. Hysterectomy was the only treatment procedure in 18 patients, of whom 84 per cent were alive and well at the end of five years. The absolute result for the entire series of 93 patients is 53 per cent.

TABLE I. CLINICAL RESULTS IN 93 PATIENTS WITH CORPUS CANCER TREATED FROM 1936 TO 1941 (THE HIGH SURVIVAL RATE FOR HYSTERECTOMY ALONE IS PROBABLY DUE TO THE SELECTION OF FAVORABLE CLINICAL MATERIAL)

TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
			NUMBER	PER CENT
Radiation alone	43	31	12	27
Radiation and hysterectomy	32	10	22	68
Hysterectomy alone	18	3	15	84
Total	93	44	49	53

Explanation should be made of the high survival rate shown for hysterectomy alone. As noted earlier, the average result for surgery as established on the basis of collected statistics is on the order of 60 per cent. The high value shown here can be attributed to selection of favorable clinical material during the transition to routine preoperative irradiation. Among the eighteen patients treated by hysterectomy alone, well-differentiated tumors were found in fourteen. The uterine cavity measured less than 4 inches in depth in fifteen of the specimens. In one patient the diagnosis of cancer was established only after microscopic examination of the uterus removed for myoma. In two patients the cancer was apparently removed by curettement, as no evidence of tumor was identified in the specimens obtained at hysterectomy. The tumor was found to be localized and measured less than 2.0 cm. in diameter in five instances. Tumors of 2.0 to 4.0 cm. diameter were found in five specimens. No measurements are noted in the records of the remaining patients, but it is obvious that the majority of the lesions were quite early and presented favorable prognoses.

More important data can be obtained by comparing the effectiveness of radium treatment by tandem with results from irradiation by multiple capsules. In Table II is shown correlation of histologic type of tumor with method of

radium treatment in relation to five-year results. Patients treated by irradiation alone are considered separately from those in whom radiation was combined with hysterectomy. Histologic classification has been made on the basis of four different types described by Healy and Cutler.¹ These have been divided numerically into adult and undifferentiated forms. A summary of results is given for each of those divisions in the group treated by radiation alone, and for those who received the combined treatment. Better results were obtained in the well-differentiated tumors in both instances. For radiation alone, the five-year survival in adult types is 30 per cent, and 25 per cent in undifferentiated forms. For radiation combined with hysterectomy the values are 74 per cent and 55 per cent, respectively.

TABLE II. CORRELATION OF HISTOLOGIC TYPES OF TUMOR WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS

HISTOLOGIC TYPE	METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
				NUMBER	PER CENT
Radiation Alone					
I-II	Tandem	12	9	3	25
	Multiple capsules	11	7	4	36
	Summary	23	16	7	30
III-IV	Tandem	6	5	1	16
	Multiple capsules	14	10	4	28
	Summary	20	15	5	25
Radiation and Hysterectomy					
I-II	Tandem	7	2	5	71
	Multiple capsules	16	4	12	75
	Summary	23	6	17	74
III-IV	Tandem	6	4	2	33
	Multiple capsules	3	0	3	100
	Summary	9	4	5	55

The effect of histologic type on end results is more variable in a comparison of tandem treatment with multiple capsules of radium. Among patients treated by irradiation alone, the well-differentiated lesions show for tandems and multiple capsules values of 25 per cent and 36 per cent, respectively. For the undifferentiated tumors the use of tandems resulted in a 16 per cent survival, but 28 per cent of those treated with multiple capsules were alive and well at the end of the five-year period. Among patients in whom radiation was used in conjunction with surgery the end results in adult types of tumor are essentially equal for radium treatment by tandem and by multiple capsules. In the undifferentiated tumors there is wide discrepancy in results for different methods of radium treatment, but the number of patients is small.

Table III shows correlation of uterine size with method of radium treatment and five-year statistics. A depth of four inches as measured by sounding the uterine cavity has been chosen arbitrarily as a method for distinguishing the smaller and larger uteri. Among patients treated by radiation alone a survival rate of 30 per cent is shown for the group with uteri measuring less than four inches in depth. The value for patients presenting uterine enlargement is 22 per cent. For treatment by irradiation used in conjunction with surgery the survival rates are 70 per cent and 66 per cent respectively.

TABLE III. CORRELATION OF SIZE OF UTERUS WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS

DEPTH OF UTERUS (INCHES)	METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
				NUMBER	PER CENT
Radiation Alone					
Less than 4	Tandem	14	10	4	29
	Multiple capsules	20	14	6	30
	Summary	34	24	10	30
More than 4	Tandem	4	4	0	0
	Multiple capsules	5	3	2	40
	Summary	9	7	2	22
Radiation and Hysterectomy					
Less than 4	Tandem	11	5	6	55
	Multiple capsules	15	3	12	80
	Summary	26	8	18	70
More than 4	Tandem	2	1	1	50
	Multiple capsules	4	1	3	75
	Summary	6	2	4	66

Upon considering the effect of method of radium treatment it is interesting to note that in patients treated by irradiation alone the use of radium tandems resulted in a 29 per cent survival in smaller uteri, but none of the four with uterine enlargement survived five years. For multiple capsules of radium the value for smaller uteri is 30 per cent, which is practically identical to that obtained for tandems, but two patients survived in the group of five with uterine enlargement. The superiority in results for multiple capsules in larger uteri is due to improvement in distribution of radiation and increase in tissue dose. In small uteri the advantage of multiple capsule treatment is less evident, because tandems may fill space within the uterus with reasonable completeness.

Analysis of results from radiation combined with hysterectomy involves consideration of only a few patients with uterine enlargement. In the smaller uteri the result from preoperative tandem of radium is 55 per cent. For multiple capsules the value is 80 per cent. Among those with uterine enlargement, one (50 per cent) of the two treated by tandem is alive at the end of five years, but 75 per cent survived after irradiation by multiple capsules.

Variation in survival rate is to be expected for both histologic type and uterine size. The attempt to compare different technique of radium treatment in correlation with only one of those factors is made complex by the effect of the other. In the small series presented here, data upon improvement in clinical results for the use of multiple capsules of radium are more conclusive if comparison is made on the basis of method of radium treatment only. In Table IV it can be seen that the use of tandems in patients treated by irradiation alone resulted in a survival rate of 22 per cent. For multiple capsules of radium the result is 32 per cent. Patients treated by irradiation and surgery show for tandems a value of 54 per cent. A total of nineteen patients received multiple capsules of radium before hysterectomy. Of that group fifteen, or 79 per cent survived the five-year period. Mention should be made of the 18 patients treated by surgery alone shown in Table I. Of that group fifteen, or 84 per cent

were alive and were at the end of the same period. The two groups are essentially equal in number and in end results. The fact that the patients receiving preoperative irradiation were not from selected clinical material indicates, however, that the average prognosis was less favorable.

TABLE IV. CORRELATION OF METHOD OF RADIUM TREATMENT WITH ABSOLUTE FIVE-YEAR RESULTS

METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
			NUMBER	PER CENT
<i>Radiation Alone</i>				
Tandem	18	14	4	22
Multiple capsules	25	17	8	32
<i>Radiation and Hysterectomy</i>				
Tandem	13	6	7	54
Multiple capsules	19	4	15	79

The effect of histologic type on end results may be largely a factor of tumor dispersion. The effect of uterine size may be due to tumor bulk and dispersion, but includes also technical problems involved in attempting to obtain a suitable distribution of radiation. Of importance in response to radiation are biologic properties affecting radiosensitivity. Disappearance of cancer as determined by examination of tissue removed at hysterectomy performed after preoperative treatment presents a more accurate estimate of tumor response. Patients presenting specimens free of cancer should have an excellent prognosis.

Data on microscopic findings in uteri removed after irradiation are given in Table V. The persistence or absence of recognizable tumor has been made on the basis of routine laboratory examination. Careful review of all specimens might reveal viable cancer in some reported previously as negative. Errors in identification should be equal for treatment by tandem and by multiple capsules. The data are suited to comparing the two methods of radium treatment in question.

Included in the table are results reported by Taylor and Becker⁹ for 119 hysterectomies done after the application of approximately 3,600 mg./hr. radiation by intrauterine tandem. The total results for the series presented here are in remarkably close agreement with those published by the authors mentioned above. Taylor and Becker found persistent tumor in 49.6 per cent of their patients. In that group the five-year survival was 44.1 per cent. For the thirty-two patients in the series reported here, persistent tumor was found in 47 per cent with five-year survival of 46 per cent. Taylor and Becker were unable to find viable tumor in 50.4 per cent of their patients who showed a survival rate of 73.8 per cent. In our series 53 per cent were without recognizable tumor, and of that number 88 per cent survived the five-year period. The destruction of tumor in the uterus is obviously an important and favorable prognostic sign. Further analysis of the series here reported shows poor results for treatment by intra-uterine tandem as compared with those published by Taylor and Becker. Improvement is shown, however, for the use of multiple capsules. Among the thirteen patients treated by radium tandem, persistent tumor was

found in ten, or 77 per cent. Of the nineteen in whom multiple capsules of radium were employed, only five, or 26 per cent, had recognizable cancer. A technique of radium treatment that will destroy cancer within the uterus in three-fourths of patients treated by that method should advance materially the clinical results obtained in cancer of the uterine corpus.

TABLE V. CORRELATION OF PERSISTENCE OF TUMOR WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS*

METHOD OF RADIUM TREATMENT BEFORE HYSTERECTOMY	TOTAL NUMBER OF PATIENTS	PERSISTENT TUMOR			UNIDENTIFIED TUMOR		
		NUMBER OF PATIENTS	PER CENT OF TOTAL	PER CENT SURVIVAL	NUMBER OF PATIENTS	PER CENT OF TOTAL	PER CENT SURVIVAL
Tandem	13	10	77	40	3	23	100
Multiple capsules	19	5	26	60	14	74	85
Total	32	15	47	46	17	53	88
Taylor and Becker ⁹	119	59	49.6	44.1	60	50.4	73.8

*Comparison is made with the larger series reported by Taylor and Becker.

Relationship can be established between tumor disappearance and histologic type. Of the thirty-two patients treated by hysterectomy after irradiation, twenty-three had well-differentiated tumors with persistent cancer found in only six, or 26 per cent. There were nine patients with undifferentiated tumors, of whom seven, or 77 per cent, showed recognizable cancer. Others have observed the greater incidence of destruction for tumors of higher differentiation. The tendency for undifferentiated forms to survive may be due in part to invasion of the uterine wall with increase in distance between some cancer cells and different sources of radium, and to greater ability for recovery of cells not destroyed completely by irradiation.

The destruction of tumor is also associated with size of the uterus. That is particularly true for treatment by radium tandem. The multiple capsule method is, however, essentially independent of uterine size. Evidence that cancer within the uterus can be destroyed in about three-fourths of the patients is shown in experience with the multiple capsule technic since the years included in this report. From 1942 to 1946 a total of thirteen patients received multiple capsules of radium prior to hysterectomy (the study was partially interrupted during the war years). The addition of those patients to the nineteen here reported presents a total of thirty-two treated by the method in question. For that number 71 per cent were without identifiable tumor.

The amount of radiation applied by radium is, of course, important in determining immediate and end results. Of the thirteen patients upon whom hysterectomy was performed more than five years ago after treatment by radium tandem, there were six who received between 3,000 and 4,000 mg./hr. radiation. Between 4,000 and 5,000 mg./hr. were applied to six of the remaining number, and one received an amount slightly in excess of 5,000 mg./hr. radiation. For that method the dose per source was on the order of 1,200 to 1,600 mg./hr. radiation. Such amounts are to be expected to produce tissue necrosis, and areas of severe damage were noted frequently.

Among the nineteen patients treated by multiple capsules before hysterectomy, there were eight who received between 3,500 and 5,000 mg./hr., and eleven in whom the total dose ranged between 5,000 and 7,000 mg./hr. radiation. The larger amounts were delivered by the more recently used technique employing an introducer for weak sources of approximately 6.0 mg. radium strength per centimeter length. In those instances the average dose per source is on the order of 450 to 600 mg./hr. radiation. An intense reaction is produced throughout the uterus, but areas of severe damage with necrosis are found rarely. The histologic changes were described in an earlier publication.¹⁵

Severe damage by radiation can produce untoward sequela. Necrosis of normal tissues in the tumor bed can result in unrestrained growth of cancer rather than control of the lesion. In clinical practice maximum and minimum tissue doses become important. In the case of radium, points near the different tubes receive the greater amount. The fall in intensity of dose is enormous within the distance of only a few millimeters. Cancer cells located at short distances from radium tubes will receive a minimum tumor dose that may be inadequate for their destruction. Improvement in distribution of radiation acts to lessen discrepancy between minimum and maximum tissue doses. For any increase in number of radium tubes contributing to the total dose there will be improvement in distribution of radiation. Due to contribution from several sources, the dose per unit becomes less important and, consequently, can be made less than would be required for the same total dose delivered by a lesser number of irradiating sources. By that means it may be possible to treat adequately a greater volume of tissue by increasing the minimum dose delivered to more distant points, without undue risk of overtreatment near radium tubes. The use of multiple capsules meets that requirement and accomplishes an improvement in results by the administration of greater amounts of radiation.¹⁶

For the method in question there is risk of uterine perforation. Such an accident has been recognized in only two instances. One has been reported previously, and occurred with the technique employing the introducer and special capsules.¹⁵ The other occurred with the use of tubes of various size and strength in which gauze was employed. In the latter instance a radium tube had become lost in the abdomen and necessitated laparotomy for removal. Neither patient with perforation survived the five-year period free of recurrence.

Hysterectomy has been performed at different intervals after radium treatment. In some patients with a lapse of only one week there has been disappearance of tumor indicating that the effect of radiation is more prompt than generally appreciated. With intervals of six weeks there has been evidence indicating recovery and renewed growth of tumor not destroyed completely. Upon that basis it appears that hysterectomy should be done as promptly as possible. The average interval has been about four weeks, but in all instances the determining factor rests upon the condition of the patient. For the most part there will be sufficient recovery from local and constitutional effects of radia-

tion by that time to permit safe performance of surgery. The use of large amounts of radiation before operation results in technical problems for hysterectomy, but those have not been of a serious order, and seem justifiable upon the basis of improvement in clinical results.

Summary and Conclusions

About 1938 a planned method of treatment was established for patients with corpus cancer at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital. The method of radium treatment was changed from one employing intrauterine tandems to a technic using multiple capsules of radium packed individually into the uterine cavity in the attempt to fill all the available space. The use of radium is preceded by the external application of x-rays. Patients suited to hysterectomy are given preoperative irradiation with both x-rays and radium.

Between 1936 and 1941, inclusive, a total of ninety-three patients with corpus cancer were treated on the ward and teaching service of the two institutions. The period of years included in the report antedates the onset of a planned method of treatment. In the earlier years radium was applied by intrauterine tandem. During the transition to regular use of preoperative irradiation, a few selected patients with favorable prognoses were treated by hysterectomy alone. Of the entire group of ninety-three patients, 45 per cent were considered inoperable due to advanced cancer, or to some constitutional disorder. The absolute five-year survival rate for the forty-three patients treated by irradiation alone is 27 per cent. For the thirty-two patients receiving preoperative x-rays and radium followed by hysterectomy the five-year result is 68 per cent. Surgery alone was used in eighteen individuals, of whom 84 per cent are alive and well for the same period. Explanation of the unusually good results from hysterectomy alone is made on the basis of favorable clinical material. The absolute five-year survival for the entire series of ninety-three patients is 53 per cent.

The attempt is made to compare the relative effectiveness of treatment by intrauterine tandem of radium, and by the use of multiple capsules. For that comparison the effect of certain biologic properties of tumor growth are also considered in their relation to end results.

Variation in survival rate is found with histologic type for treatment by radiation alone as well as in conjunction with hysterectomy. Better results were obtained in the more highly differentiated forms. An improvement in clinical results is shown for the use of multiple capsules.

Variation in survival rate is found also with size of the uterus. For treatment by radiation alone the results in uteri of small size were about equal for tandems and multiple capsules. In those instances a linear arrangement of radium tubes may fill the uterine cavity with reasonable completeness. Among the four patients with large uteri, however, there are no survivors for treatment by x-ray and radium tandem alone. The use of intra-uterine tandems in conjunction with surgery resulted in survival of about half of the patients. Only two showed enlargement of the uterus. The results from multiple capsules and

hysterectomy appear essentially independent of uterine size. About three-fourths of each group survived the five-year period.

Despite the fact that survival rates are affected by both histologic type and uterine size, and improvement in clinical results can be shown for the use of multiple capsules by comparison made on the basis of method of radium treatment only. Among patients treated by radiation alone the use of intrauterine tandems resulted in survival of only 22 per cent, but 32 per cent of those irradiated with multiple capsules are alive and well at the end of the five-year period. For treatment by irradiation and hysterectomy the use of intrauterine tandems resulted in survival of 54 per cent, but the value for multiple capsules of radium is 79 per cent.

More reliable than histologic type or uterine size in establishing the clinical result to be expected is the persistence or disappearance of tumor within the uterus after preoperative irradiation. Among the thirty-two patients treated by hysterectomy after the use of x-rays and radium, persistent tumor was identified in 47 per cent. Of that group only 46 per cent survived the five-year period. Among the patients in whom no tumor was identified the survival rate is 88 per cent. Persistent tumor was found in 77 per cent of the patients irradiated by tandems. Only 26 per cent of those in whom multiple capsules were employed showed viable cancer in the specimen removed at hysterectomy.

In view of the 88 per cent survival for patients without recognizable tumor within the uterus, it should be noted again that no residual cancer was recognized in three-fourths of specimens previously irradiated by multiple capsules of radium. Furthermore, fifteen (79 per cent) of the nineteen patients treated by multiple capsules and hysterectomy are alive and well after five-years of observation. Those patients were not selected clinical material as were the eighteen treated by hysterectomy alone. Having attained essentially equal results in both groups seems to establish for the small series an improvement in clinical results for preoperative irradiation by multiple capsules of radium.

Discussion is given upon the improvement in distribution of radiation and in tissue dose for multiple sources of radium within the uterus. By means of that method it has been practical to increase the total amounts of radiation employed. Accidental sequelae in two patients are described, and the interval of time between preoperative irradiation and hysterectomy is discussed.

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Discussion

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—The crux of this presentation lies in the question: is the multiple small source intrauterine distribution of radium worth the trouble and the risk that it entails? General dissatisfaction with the older methods of application has stimulated the introduction of many devices that aim at more accurate radium placement. In the effort to accomplish this objective we use a modification of the Crossen wire technique with moderate success, as evidenced by x-ray study. A total of 5,000 to 6,000 milligram hours of radium is administered in one or two sittings by distributing seven to ten capsules of 10 milligrams each in the uterine cavity. By a simple maneuver we place one or two capsules across the top of the cavity at right angles to the cervical canal. This technique has not been in use sufficiently long for us to judge the results in terms of survival rates. We can say, however, that we are impressed with the more uniformly disseminated effect of the irradiation as we study the removed uteri.

Dr. Arneson states that his plan is a modification of the Heyman packing method. He is to be congratulated upon the first report in this country concerning the clinical results of this procedure. While his samples are not large enough to serve as conclusive statistical evidence, they do suggest that his plan offers great promise. Undoubtedly, it is far more troublesome than the older method. Furthermore it is slightly more dangerous, as indicated by two perforated uteri in the present series and three similar accidents that Heyman reported to have occurred during a thousand applications. When the obvious theoretic advantages of the procedure are supported by highly suggestive evidence of its clinical superiority, the bother and the slight additional risk seem to be compensated fully. (*The British Journal of Radiology*, March, 1947) Heyman advanced his five-year survival rate from 45 per cent in 354 patients to 64.9 per cent in 316 patients by means of his packing method. By condensing Arneson's charts we see that following the use of multiple capsules his salvage rate rose from 35 per cent to 52 per cent. The apparent explanation for this improvement is seen in Tables III and V, based upon seventy-five patients who were treated by either irradiation alone or by irradiation and surgery. In Table III, forty-three patients received only irradiation and the survival figures were 10 per cent better following multiple capsules than they were after the tandem application. Of thirty-two patients who were treated by surgery after irradiation the packing technique was followed by a 25 per cent better survival rate. In Table V, which depicts persistence of the tumor after irradiation, Arneson found the growth to remain three times as frequently after tandem sources than it did after multiple sources. In the same table his figures indicate that the chance of survival is almost twice as great if the tumor is destroyed by irradiation prior to operation.

Consideration of these interesting figures, although they are based upon small groups of patients, does suggest that some form of intrauterine multiple small source radium distribution is a worth-while procedure.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Arneson and his associates have presented convincing evidence of the fact that preoperative irradiation with radium offers better end results in the treatment of fundal carcinoma than does primary surgery alone. This is in line with a belief that we have entertained personally for many years, a belief that has been shared by others working in this particular field.

This study leads into several interesting by-ways of investigation with respect to the importance of tumor gradation, size of the uterus, persistence of tumor after irradiation, and irradiation in relation to prognosis. Certain valid correlations, or at least a trend toward such correlations, seem to have been established.

Of most importance, and certainly as regards the life of the patient, is the relatively higher survival rate attained by Dr. Arneson through the use of the multiple capsule technic

in preference to the older tandem technic. However, one must bear in mind that perhaps two factors may perhaps influence these improved statistics.

First, it is likely that the more recent use of the multiple capsule method when compared with the tandem method, would naturally present a higher survival rate among those patients more recently treated, when compared with the patients treated earlier, and who are now in the older age group. Second, the additional use of external irradiation before the preoperative radium application.

Nevertheless, when another factor is taken into consideration, namely, persistence of tumor in the removed uterus, it certainly seems that multiple sources of radium are distinctly advantageous in destroying the malignancy and retarding recurrence.

I would like to know what the incidence of concomitant fibromyomas was in the series presented. Their presence often accounts for the uterine enlargement to the exclusion of the cancer itself, especially with respect to the distortion of the uterine cavity.

In relation our own experience with this problem (Jefferson Hospital), I shall confine myself to but one phase, viz., results with the tandem technique where a planned procedure for the treatment of fundal cancer was possible. The broader problems associated with the management and treatment of fundal carcinoma in general have been taken up in the recently published article of ours that Dr. Arneson referred to. It has been our feeling at Jefferson Medical College Hospital that the tandem technique of intracavitary radium possesses distinct advantages apart from the actual treatment of fundal cancer itself, and especially in one respect. The possibility of endometrial malignancy must naturally be considered abnormal uterine bleeding at the menopause. Visual and palpatory examination offers nothing conclusive. In the management of such patients, radium therapy is often ideal. Accordingly, we always have radium capsules (25 or 50 mg.) available when the diagnostic curettage is to be carried out. An excellently prepared histologic section of the curettings is then available in four hours or less. An intracavitary application of radium is made immediately following the curettage, and in tandem if the character of the uterine cavity permits. Should the report prove benign a suitable dosage is decided upon, following which the capsule or capsules are readily removed; if malignant, dosage adequate for cancer can be employed, and adequate surgery follows in about six weeks if the patient is a suitable risk. Such a procedure, it seems to me, would not be so easily carried out with the multiple units described by Dr. Arneson.

Employing the plan mentioned, I may state that during approximately fifteen years we have treated in this fashion seventeen patients with fundal carcinoma eligible for five-year statistics. Fifteen are living from five to fifteen years later, indicating a survival rate of 89.2 per cent. In approximately 50 per cent, residual malignancy was present. External irradiation has played no part whatsoever in the treatment of these selected patients, and there was no primary mortality.

During the past four years or more, but not eligible for five-year evaluation, we have treated thirty-nine additional patients with fundal carcinoma in this way, with thirty-seven survivors to date, also without primary mortality.

On the basis of this accomplishment, I am loath to change our present plan of therapy for fundal cancer, but I am frank to confess that Dr. Arneson's valuable presentation may change our viewpoint to some extent, especially with respect to those patients in our consecutive series who are not suitable for subsequent surgery for one reason or another.

DR. DANIEL G. MORTON, San Francisco, Calif.—With regard to the effort to develop a method whereby radioactive substances may be applied to the inner surfaces of the uterus in endometrial cancer in a more efficient manner than is afforded by a simple tandem of two, three, or four pieces of radium, I should like to report briefly an experiment which we carried out at the University of California in 1943 and 1944. At that time, due to the development of the cyclotron, certain radioactive solutions, namely radioactive phosphorous and radioactive strontium, became available. It occurred to us that we might possibly use these solutions to effect an even distribution of radiation within the uterine cavity. A solution should have the property of filling out all of the crevices and interstices of a growth in a manner which

could not possibly be duplicated in any other way. The main problem, of course, would be to distend the cavity fully and yet retain the solution within the uterus without leakage through the tubes or from the cervix. In order to do this we used the water-containing unit of the Foley catheter—not entirely satisfactory, but approximating what we sought; i.e., a very thin rubber sac which could be distended under pressure after introduction. Presumably, whatever the shape of the cavity, it would be filled out. Anywhere from 4 to 13 c.c. were used in the four cases in which this method was used. The material was left in place for forty-eight to seventy-two hours. We had an opportunity to examine the uteri later in all cases, because subsequent hysterectomy was performed in three cases, and an autopsy was performed in the fourth case, when the patient died only a few weeks later.

In all cases it was found that there was superficial necrosis of the growth, or of the fibromuscular tissue of the uterine wall, in areas where no tumor existed and the endometrium was thin. The maximum depth of the reaction was about 2 mm. At greater distances from the surface “healthy” cancer cells remained. So our experiment was a failure, but we believe that the idea is a good one and susceptible of development. The solutions we used give off B rays only—not gamma rays. We believe that the failure to penetrate deeper is related to this fact.

It now appears that other radioactive solutions will become available; e.g., radioactive cobalt, from which gamma rays emanate. We plan to try some such solutions. The matter of dose and mode of application will of course require considerable thought. However, the general idea we believe to be worthy of further research.

DR. CURTIS F. BURNAM, Baltimore, Md.—We have been using multiple sources of radiation in Baltimore for many years: in fact, my first paper published in the early 20's on the treatment of adenocarcinoma of the uterine body was on cases treated in this way. In Curtis' *Gynecology* the method is shown. There can be no doubt that in uterine body carcinoma irradiation more effective treatment is obtained by multiple sources than by tandem arrangement.

We feel, too, that in body carcinoma it is very important to irradiate the cervix and the vagina. It is extraordinary how often a metastasis occurs in the vagina from cancer of the body of the uterus.

The dosage that we have employed has varied with the size of the uterus and the character of the cavity. We never use ordinary tandems; our sources are not radium but radon, and we use bulbs 2 to 3 mm. in diameter. The dosage in a small uterus is hardly ever over 2 gramme hours. In large uteri where there are fibroids for example, we give twice that much or more. It is important to take the individual unit and to calculate the dosage in the volume around it.

I have not had much success in treating body cancer with x-ray. After adequate intra-uterine radiation, an additional amount of x-ray has greatly increased small bowel and sigmoid injuries, i.e., an amount of x-ray that could be beneficial.

We usually use in radon the equivalent of 2 Gm. of radium. The treatment in a small uterus can be given in one hour. Also, there are many cases of body carcinoma which have complications. What would you do, Dr. Arneson, in a case of pyometrium? We have tried to clear up the infection and then use intrauterine radium. I am convinced that the best method of treatment in cancer of the uterine body is the combination of radiation and operation.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I appreciate the fact that Dr. Arneson is talking specifically about intracavitary radiation. I am moved, however, to say just a word about another form of radiation, namely deep x-ray, as a supplemental means of treating corpus cancer. Our aim is to cure the greatest number of patients. Radiation by the intrauterine placement of multiple capsules is one of the better methods of achieving good results, especially when used in combination with operation later on. However, we should not be blinded to the value of high-voltage x-ray treatment in the management of this condition. We have used x-ray as a preoperative measure in the management of corpus car-

cinoma in our clinic (University of Michigan Hospital) for about fifteen years. At the last meeting of this Society I reported on approximately 100 cases so treated and pointed out that by this method we had obtained 77 per cent five-year and 65 per cent ten-year survivals.

I believe the use of x-ray gives more thorough parametrial treatment than can be accomplished by intracavitary radium.

DR. SUBODH MITRA, Calcutta, India.—I would offer some criticism of Dr. Arneson's paper in that the evidence from this material is not sufficient to draw any statistical conclusion. In one of the groups he had four cases and we do not know how many of those are dead, and how many lost sight of; so it is very difficult to express any opinion in that respect.

The next point to be decided is which is the best method of treatment for carcinoma. The application of radium by capsules is as good as an operation itself. I have seen the work of Dr. Heyman who has found very satisfactory results by using multiple capsules alone without any subsequent operation. I have also had some operative cases of my own with good results. Under the circumstances one must think seriously whether this application of multiple capsules should be supplemented by another operation. We use subsequent deep x-ray therapy only when we do the operation or give the radium treatment.

Dr. Miller offered a very valuable suggestion that x-ray does help as well as radium in treating these cases of carcinoma.

DR. ARNESON (Closing).—On a critical basis it can be said that the method of treatment in question is cumbersome, expensive, and not without risk to the patient. We have worked on the hypothesis that risk of intestinal injury is greater for x-rays than for radium. For that reason the amount of roentgen treatment has been less than is generally employed. It is sufficient, however, to produce tumor changes and to decrease the amount of infection always present. By that means the patient is better prepared for intrauterine radium, but it is not to be implied that a preliminary course of x-rays will eliminate pyometria. Any collection of pus within the uterus must be drained before radium is applied.

The effectiveness of treatment depends upon the distribution of radiation, the tissue dose obtained, and the biologic properties of the lesion. Both maximal and minimal doses falling within the tumor-bearing region are important. Maximal quantities must be less than amounts apt to produce extensive tissue damage. Minimal doses must be adequate for the control of tumor. In combinations of x-ray and radium treatment the greater amounts of radiation will fall along points near the radium tubes. If the number of irradiating sources is increased, then the contribution required from a particular tube is made less. By that means a more uniform distribution of radiation is obtained, and the minimal amount falling within the tumor can be increased. It is on that basis that Dr. Burnam has used bulbs of radium within the uterus, and that Dr. Heyman devised his technic. Dr. Morton's discussion is particularly pertinent. By the use of solutions of radioactive isotopes in flexible containers, the application can be molded into a shape corresponding to the uterine cavity. The intensity of radiation would vary only with the magnitude of projections into isolated regions.

In teaching procedures we encourage students to think in terms of the dose per source. To express treatment by the total number of milligram-hours radiation is no more correct than to attempt description of a surgical procedure on the basis of the time required for operation. We believe that the use of multiple capsules has been established as an effective clinical procedure. We hope to gain further increase in the number of radium tubes employed, with decrease in the amount of radiation contributed by each source. Mention should be made of work by Dr. Nolan. By means of special film he has studied photographically the zones of effect within phantoms for different methods of radium application. In clinical practice the use of preoperative irradiation has interfered with subsequent surgery in only a very few patients.

HIGH LYMPHADENECTOMY AND SYMPATHECTOMY IN CARCINOMA OF THE VULVA*

EDWIN M. ROBERTSON, F.R.C.O.G., F.R.C.S. (EDIN.), F.R.C.S. (C),
KINGSTON, ONTARIO

(From the Department of Obstetrics and Gynecology, Queen's University.)

THE successful treatment of carcinoma of the vulva differs in no way from that of carcinoma in other sites in that the primary lesion, the spreading growth, and the metastases in lymph nodes must be completely destroyed or eradicated.

Because the malignant vulvar tumor is situated on a part of the body which has an enormously widespread lymph drainage system, the exact limits of surgical excision required are difficult to estimate, as are the sites and dosage of radiation.

The surgeon may excise a primary tumor entirely and many near-by malignant lymph nodes, but he never knows how much of the metastatic growth is left behind. By radiation a wide area can be covered and scattered malignant tissue destroyed but recurrences indicate that the lethal rays do not strike all the cancer cells in every case.

Apart from the simplification of the many problems associated with the cure of carcinoma which earlier reporting would bring, it seems logical to conclude that more extensive surgery and heavier and wider irradiation must improve the results of treatment of carcinoma.

The reasonable limits of surgical procedure and radiation therapy are always extending side by side with discoveries and advances in many other scientific fields translated into improvements in pre- and postoperative care and operative technique. At the moment, however, it seems that the radiation therapy of vulva carcinoma and lymph node metastases, in the groin for example, is more limited than surgical excision of the affected parts and so it is that vulvectomy and lymphadenectomy are the more favored procedures.

With those premises in mind, a recent case of epithelioma of the vulva was treated by vulvectomy, inguinal, pelvic, and lumbar lymphadenectomy. Lumbar sympathectomy was also performed as a prophylactic measure against arterial spasm, venous thrombosis and excessive sweating.

The patient concerned, Mrs. H., aged 37 years, was referred to me on Feb. 19, 1947, by Dr. Baker of Campbellford, Ontario, for a nonhealing ulcer of the vulva which had been recognizable for at least one and one-half years. The carcinoma was 7.5 cm. long and occupied the right side of the vulva, stretching from the clitoris to the perineum, and from the outer edge of the labium majus to the urethra and just inside the vagina.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

The right subinguinal lymph nodes were markedly enlarged and somewhat fixed. The left subinguinal nodes were just barely palpable. Aside from the discomfort of the vulvar growth, the patient neither felt unwell nor had she lost weight.

Vulvectomy was performed on February 21, in the course of which more tissue was removed from the right side than the left. The anterior edge of the incision on the right side passed medial to the insertion of adductor longus muscle, and was placed far enough back to allow removal of some of the fatty tissue emerging from the ischiorectal space. Both on the right side and on the left the fascia over the adductor muscles was laid bare, and within the area defined by the pubic rami the soft tissue was cleared away until the branches of the pudendal artery could be clamped as they emerged from under the edge of the bones. Medially, the incision partially ringed the urethra and then entered the vagina for about one-half inch.

In order to cover the large bare area thus exposed, the adjacent skin was undercut in all directions and, in addition, on the right side a large flap was cut from the thigh and turned medially so that its upper edge became the right side of the vaginal introitus.

Postoperative treatment followed our usual routine, which includes pressure dressing to prevent accumulation of tissue fluid, indwelling catheter for five days, prophylactic sulfadiazine for five days, penicillin up to 300,000 units, early ambulation, bed exercises, and the use of the lavatory.

The first lymphadenectomy was not performed until thirty-five days later, by which time it was hoped that any reactionary changes in the inguinal glands or those higher in the chain would have died down. The steps of the operation were based on Taussig's modified Bassett operation.¹

The left side was done on March 28. Exposure for this operation is made by an incision about seven inches long from a point one inch above and medial to the anterior superior iliac spine, and curving down to cross the middle of Poupart's ligament and continue in the line of the femoral vessels. Block dissection of the fat, nodes, and areolar tissue is begun about two inches from the termination of the saphenous vein. The vein is followed, ligated, and cut near its junction with the femoral vein. The fat and nodes are then dissected from the fascia of the anterior abdominal wall, and at the external abdominal ring the round ligament is tied and cut. The tie allows of easy identification later in the operation. The block of tissue is now dissected from all sides toward the fossa ovalis. It seems that the superficial veins and arteries are easily clamped in this way, and there is no danger of tearing the saphenous vein at its deepest point.

The femoral sheath is then opened, and any nodes lying medial to the vein are removed. The femoral canal is identified, and the gland occupying its proximal end is pulled up with an Allis forceps and removed also.

The inguinal canal is now opened, and this can be safely done by pulling on the round ligament and cutting over it with a knife. The epigastric vessels come into view on the deeper part of the round ligament and medial to it, and are tied off and cut after the conjoint tendon has been snipped with scissors. Lateral extension of this extraperitoneal opening can be obtained by cutting the fibers of the internal oblique and transversalis muscles and fascia.

With this exposure the intact peritoneal sac can be gently stripped inward from the underlying iliac vessels and lymph nodes and, although the hypogastric and common iliac nodes lie very deeply, they can be easily reached.

In this case none of the inguinal or the iliac nodes on the left side appeared to be enlarged, and it was later reported that none showed malignant tissue.

The operations of right lumbar sympathectomy and lymphadenectomy of the right lumbar, pelvic, and inguinal nodes were performed four days later.

In reviewing all the hazards of the operation in this case, hemorrhage and deep infection were regarded as possible but not probable complications, as they would be of any such procedure. A recent experience of encountering arterial spasm in the lower limb following extensive dissection of malignant nodes adherent in the region of the large vessels prompted very careful consideration of steps which could be taken to circumvent the recurrence of such an accident in similar circumstances.

In any event, hemorrhage and infection are conditions about which, perhaps, there is not the same prophylactic uncertainty as there is about such potentially serious complications as postoperative vascular spasm, thrombophlebitis, phlebotrombosis, and pulmonary embolism.

The manipulations of dissecting areolar tissue and lymph nodes surrounding the large vessels have to be performed very gently, for obvious reasons. Even with the greatest care, it is not uncommon to observe hardening, presumably spasm, of the iliac vessels, and it is known that injury of blood vessels sometimes results in prolonged vascular spasm. Oesner and DeBakey² are convinced that the clinical manifestations of inflammatory thrombosis are due to vasospasm of the arterial and venous systems beyond the lesion caused by the irritation of the venous segment affected.

Although the actual cause of venous thrombosis is not known, almost all records show that pelvic operations, especially in women, are commonly the preceding condition. There are undoubtedly many factors at work, but changes in the composition of the blood, narrowing of the vessel lumen, and stasis are etiologically very important.

As regards the possibility of producing vascular irritation and its consequences during the course of an operation, the Bassett-type of lymphadenectomy in either vulvar cancer or cervical cancer, both conditions in which infection may be present in lymph nodes and the surrounding tissues, is one which involves more handling and possible trauma of the large veins and arteries than almost any other pelvic operation in women, excepting that for cancer of the rectum. It seems logical, always assuming that there is some connection between distant thrombosis, widespread vascular spasm, and such surgical procedures to perform lumbar sympathectomy before or at the time of the pelvic operation, the primary effect of which is to produce vasomotor paralysis. It is well known, of course, that in the treatment of established thrombophlebitis, local anesthetic sympathetic block has been advocated and, also, to relieve the pain, swelling, and ulceration of chronic thrombophlebitis, lumbar sympathectomy is now widely practiced.

Shortly after sympathectomy, the extremity is dry, warm, and of good, if not a little deeper, color than before. The increased warmth is due to a marked and sustained increase in blood flow to the limb. The dryness is due to pseudomotor paralysis which completely inactivates the sweat glands.

These reactions, increased blood flow and inactivation of the sweat glands, might be considered of great advantage in vulvectomy and groin dissections for reasons not directly connected with the prophylaxis of vascular injury and vasospasm, namely, the promotion of better healing of skin flaps through in-

creased blood supply, the reduction in moisture from sweating, lessening of concomitant skin infection, and, also, avoidance of postoperative fissure at the vaginal introitus.

The extension of the range of the right lymphadenectomy to include the lumbar nodes was undertaken partly because lumbar sympathectomy was going to be done and the lumbar chain of lymph nodes would be easily accessible, and partly because these nodes form the next stage after the iliac group in the natural spread of carcinoma, even although such metastasis appears to be a late one.

In this case the retroperitoneal approach to the sympathetic chain and the lumbar glands was made through an incision starting midway between the last rib and the iliac crest and ending one inch medial to the lateral edge of the rectus muscle opposite the umbilicus. The technique of White and Smithwick³ was otherwise closely followed. The second, third, and fourth lumbar ganglia were removed with their connecting branches, and thereafter the lumbar lymph nodes were dissected out from a point at the level of the second lumbar vertebra. The upper end of the chain was cut, but the lower end was not severed, and when the packing which had been put in to keep the peritoneum and ureters displaced medially was removed, the mass of glands was tucked down toward the pelvic brim and the incision was closed.

Inguinal and pelvic lymph node dissections were then performed as described for the left side and toward the end of the operation, when the iliac nodes were freed, it was possible to pull down the lumbar chain which had already been separated.

Anesthesia for this operation consisted of spinal pontocain, 12.0 milligrams augmented during the latter half of the operation by half a gram of pentothal sodium given intravenously. The operation lasted three hours. All the glands were sectioned and squamous epithelioma was found in the inguinal and iliac glands, but malignant tissue was not discovered in the glands from the lumbar chain. Routine orders for postoperative care were carried out as usual and no complications occurred. The right leg was slightly pinker than the left and skin temperature was about one degree higher on the right than on the left.

Discussion

The three operations described constitute a heavy risk to the patient. There seems little doubt that with the unfortunately late reporting of many women with vulvar carcinoma, the pelvic lymph nodes are often involved, and because there is no means of knowing in which case this has already occurred, those lymph nodes should be excised routinely.

As Taussig has shown, there is little difference in his percentage cure rate between those who have and those who have not malignant metastases in these nodes. Watson,⁴ however, treated a series of twenty-five cases of all stages of the disease without pelvic lymphadenectomy and obtained 40 per cent five-year survival, which is 15 to 20 per cent less than that obtained by Taussig who invariably, in a selected group of cases, performed lymphadenectomy. As Watson says in his report, "If operable cases have involvement of this (pelvic) group of nodes as constantly as is indicated by some observers, the survival of any of our cases is unexplainable."

The advanced age of many women suffering from carcinoma of the vulva must of itself restrict operative procedures to a minimum, but, on the other hand, it is not the young but the aged who already may have an impaired vascular system who are more likely to develop the vascular complications of surgical operations.

Descriptive details of postoperative complications and postmortem reports on those who have died as a result of surgical treatment of this disease are exceedingly scanty in the literature, and therefore information on the relative frequency of hemorrhage, infection, thrombosis, fatal embolism, surgical accidents, etc., is not available in our small clinic (Kingston General Hospital) on which some justification for sympathectomy as a prophylactic measure can be based. If, however, the surgery of genital carcinoma is to become as radical as it is rapidly becoming in many other branches of surgery of carcinoma, then gynecologists may have to take cognizance of the risks of trauma and infection incidental to handling the large vessels when they, themselves, undertake such major procedures as lymphadenectomy.

Extension of surgical extirpation of a primary growth to removal of, first, the inguinal lymph nodes and, then, the pelvic nodes, is now an accepted practice, and it has been enabled by vast advances in surgical treatment. One wonders how much farther "cutting for cancer" will go.

It was not without very careful consideration that the accepted limits of surgical treatment of vulvar carcinoma were exceeded in this case, but the relative youth of the patient, the large size and prolonged history of the growth, confidence in the safety of modern surgical procedures to avoid shock and infection, and a hopeful confidence, perhaps quite misplaced, in concomitant sympathectomy as a means of lessening the chance of development of thrombosis and embolism, all were strong impelling influences.

It must be admitted that unilateral dissection of the lymph nodes in any region within the sphere of metastases of carcinoma of the vulva is at first sight unsatisfactory, but, in this case, because the lymph nodes in the inguinal and pelvic zones were free from cancer, it was felt that it was most unlikely that the left lumbar chain would be invaded. This conclusion, rightly or wrongly, was readily acted upon in view of the fact that retroperitoneal surgery of the glands and nerves is not frequently practiced.

Summary

1. One case of carcinoma of the vulva, occurring in a woman 37 years of age, for which wide vulvectomy, bilateral inguinal and pelvic lymphadenectomy and right lumbar lymphadenectomy and lumbar sympathectomy were performed, is described.

2. The reasons for performing lumbar lymphadenectomy and lumbar sympathectomy as a prophylactic measure and its method of performance are presented and discussed.

3. Similarly, the reasons and a method for extending lymphadenectomy in carcinoma of the vulva to include the lumbar glands are given.

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Discussion

DR. DANIEL MORTON, San Francisco, California.—It is fortunate that cancer of the vulva is one of the rarer types of pelvic malignancy, since the opportunity to treat it in an early stage presents itself rather infrequently. Furthermore, the treatment is by no means satisfactorily determined. Taussig's results, last reported in 1940 (at a meeting of this Society), are the best I know of. As you are well aware, he advocated complete vulvectomy plus bilateral resection of the superficial and deep inguinal nodes, the femoral nodes, and the obturator node, though he minimized the importance of the latter. Others have combined vulvectomy with x-radiation of the glands mentioned. Radiation of the local lesion has been used, and not without success, but produces so much havoc in the vulval skin that this method is usually reserved for inoperable cases. Few have followed a consistent policy, however, and incomplete operations are frequent. Taussig estimated that about 70 per cent of cases were operable. He found that approximately 40 per cent of his cases had regional gland involvement. He had five-year cures in 58.5 per cent of those completely operated upon, and 32 per cent of the total of 155 cases.

Now Dr. Robertson has devised an even more radical operation. There is no doubt that the more radical the procedure the greater will be the chance of eradicating all of the cancer. However, one finally reaches a point of diminishing returns. I believe that this is so for the operation described, at least in the usual case. While the removal of even isolated distant metastases is sometimes indicated and curative, cancer operations (any organ) which aim to remove glands much beyond the first line of defense (represented for the vulva by the inguinal and femoral glands) are rarely successful because (1) the mortality goes up, and (2) if second stage glands are involved, even more distant structures are also likely to be involved.

With regard to the mortality, it must be remembered that the majority of women with vulval cancer are rather old. While improved anesthesia and pre- and postoperative care will undoubtedly allow such a radical operation in most cases without immediate "on the table" mortality, these women are bound to be more subject to pneumonia, infection, and possibly to embolism.

It is possible that in occasional cases, e.g., in young women, as in the case described by Dr. Robertson, who would otherwise have a chance for many years of life, such an operation might be indicated. In this connection, one might consider the use of x-radiation which would certainly have as much rationale as its use in cervical cancer, so far as nodes are concerned. You may recall that we demonstrated a much lower incidence of glandular involvement in cervical cancer cases *after* x-radiation, than without it.

With regard to sympathectomy, I find myself unable to comment. I have had no experience along these lines. Offhand, I believe that I would rather fear the very complications which Dr. Robertson seeks to avoid, due to the necessarily rather rough manipulation of the vessels incident to sympathectomy.

I am unable to quarrel with Dr. Robertson for treating a case of vulvar cancer in a young woman in the way in which he has described. However, I do feel that such an extension of surgical maneuvers will rarely be indicated.

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Robertson emphasizes earlier recognition of the lesion in carcinoma of the vulva in order to improve the results, and this is in accord with the recommendations of those interested in the treatment of cancer, no matter where situated. Dr. Robertson points out that more extensive surgery and heavier and wider irradiation may also give better results, with which I heartily agree. Modern technique and prep-

aration, as well as improved postoperative care, allow more extensive operations in the treatment of cancer, such as a radical operation, unthought of a quarter of a century ago.

In so far as carcinoma of the vulva is concerned, this condition is usually found in old people, a number of whom are poor surgical risks; it is, therefore, advisable to do the operation in stages. Some do the lymphadenectomy first and later the vulvectomy. Dr. Robertson starts with the vulvectomy and does the lymphadenectomy sometime later. Taussig popularized the Bassett operation in this country and made it the accepted method for treatment of carcinoma of the vulva. It is agreed by most gynecologists that in this particular disease, surgery is preferable to irradiation by means of radium and x-ray.

Dr. Robertson presents a case report of carcinoma of the vulva in a woman 37 years of age, on whom he performed a vulvectomy, inguinal, pelvic, and lumbar lymphadenectomy, and followed that by lumbar sympathectomy as a prophylaxis against arterial spasm, venous thrombosis, and excessive sweating, it being Dr. Robertson's belief that by preventing excessive sweating the flaps are more readily healed, and this subsequently proved to be the case. In the dissection of the inguinal and femoral glands the saphenous vein was ligated and cut. Dissection of the lumbar glands is a more extensive step of the operation and one with which I am not familiar. I have personally had no experience with lumbar sympathectomy in connection with the management of carcinoma of the vulva.

The sulfonamides and antibiotics in the prevention of infection play a role in the postoperative care of this lesion as they do in other types of surgery. Spinal anesthesia, followed by pentothal intravenous anesthesia, as employed in Dr. Robertson's case, should prove to be satisfactory, but my personal preference would be for continuous spinal anesthesia.

I would be interested in knowing the end-result of this extensive operation.

DR. ARTHUR H. CURTIS, Chicago, Ill.—May I ask Dr. Robertson if he uses dicumarol?

DR. ROBERTSON (Closing).—No, we do not use dicumarol. My experience with dicumarol postoperatively has not been disastrous, but we have experienced massive hemorrhage after its use in two cases, and therefore would not use it again. After this rather extensive discussion I think we would advocate against using any such drug unless forced to do so.

THE DETAILED ANATOMY OF THE PARAURETHRAL DUCTS IN THE ADULT HUMAN FEMALE*

JOHN W. HUFFMAN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School,
and the Gynecological Service of Passavant Memorial Hospital)

SKENE'S¹ historic presentation in 1880 established the clinical significance of the paraurethral ducts. Prior to that time the presence in the human female of a structure homologous with the prostate had been discussed since Galen² first, although incorrectly, described such an organ. The evidence that the paraurethral ducts and their glands are homologues of the prostate has come to be generally accepted. However, the extent and the detailed anatomy of these structures still remains a controversial matter, and a review of the present-day literature confirms Everett's³ statement that there is no unanimity of opinion on the subject of paraurethral and urethral glands. The purpose of this presentation is to describe the paraurethral ducts and glands of several adult human females as studied in serial sections and as demonstrated in wax model reconstructions in an effort to portray, at least in part, the anatomy of the prostatic homologue in the adult human female.

Galen, in describing the homology of the female genitals, mentioned a prostatic gland. However, it would appear from his description that he was not alluding to a gland about the urethra, but to some structure near the Fallopian tube. Interestingly enough Galen pointed out that Herophilus first had referred to the similarity of the male and female genitals. Riolan,⁴ in commenting on Galen's description, mentions that only Piccolomini's observations were in accord with those of Galen, and that other early anatomists disagreed with Galen's concept that a homologue of the prostate exists in the human female. de Graaf⁵ in 1672, gave the first description of glands and ducts about the female urethra. In "De mulierum organis generationi inservientibus" he described large ducts opening into the female urethra near the meatus and also above these ducts smaller crypts which drain the female prostate. In an illustration, de Graaf showed a glandular structure of considerable size surrounding the urethra with two ducts which are comparable to those described by Skene two centuries later. De Graaf called this gland with its ducts the female prostate. Sixty years later Astruc⁶ (1737), in a treatise on venereal diseases, described a prostate which surrounds the female urethra and also small lacunae along the sides of the urethral canal. Winslow⁷ (1775) mentioned smaller lacunae and one larger duct in the female urethra. Boyer⁸ (1797) described in some detail the openings of mucous secreting glands at the urethral meatus and in the urethral mucosa. Cruveilhier⁹ (1844) stated that there was no prostate in the female, but that there were numerous urethral mucosal crypts or lacunae opening into the urethral mucosa. In 1853 Virchow,¹⁰ in describing calculi he had noticed in the female urethral glands, alluded to these glands as homologues of the prostate.

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Robin and Cadiat¹¹ found no glands about the female urethra and doubted the existence of a prostatic homologue.

Skene's original description and its accompanying illustration are still the basis for most descriptions of paraurethral ducts in the current literature. In his original article Skene wrote: "Upon each side near the floor of the female urethra there are two tubules large enough to admit a No. 1 probe of the French scale. They extend from the meatus urinarius upwards from three-eighths to three-quarters of an inch . . . the tubules run parallel with the long axis of the urethra . . . they are located beneath the mucous membrane in the muscular walls of the urethra . . . the mouths of these tubules are formed upon the free surface of the mucous membrane of the urethra within the labia of the meatus urinarius. The location of the openings is subject to considerable variation according to the condition and form of the meatus. . . The upper ends of the tubules terminate in a number of divisions which branch off into the muscular walls of the urethra."

Following Skene's description, the origin and even the presence of urethral ducts and glands came in for considerable discussion. To some extent this discussion has persisted to the present time. In 1889 Tourneaux¹² pointed out that the urethral glands of the female, together with the paraurethral ducts, are homologues of the prostate. Oberdieck¹³ and later Aschoff¹⁴ found deep prostaticlike lacunae along the female urethra. Felix¹⁵ considered the paraurethral glands to be prostatic homologues. In 1901, Pallin¹⁶ pointed out that the glands of the female urethra were homologous with that portion of the prostate arising cephalad to the urogenital sinus. In 1911, Wyatt¹⁷ concluded that the glands surrounding the female urethra are prostatic homologues, and that the female urethra is a counterpart of the male prostatic urethra. Johnson,¹⁸ in 1922, after constructing wax models of several embryonic urethras, felt that the paraurethral ducts are unquestionably homologous with male prostatic ducts.

Hunner¹⁹ described the openings of numerous mucous glands along the inferior urethral wall and noted that the glands tend to increase in size and complexity toward the outer end of the urethra. He quoted Schuller²⁰ as having found a third but smaller gland or tubule lying in the midline between the two described by Skene.

In recent years interest has been renewed in this problem, and some disagreement has occurred relative to the presence of urethral glands, other than Skene's ducts, and as to their extent and importance. Deter, Caldwell, and Folsom²¹ have presented evidence that there are tubular glands about the posterior urethra and that they are clinically important in urethral disease. MacKinsie and Beck²² after examining numerous longitudinally sectioned urethrae of children and adults reported that true urethral glands do not exist in that third of the urethra nearest the bladder. They found that while the paraurethral glands may encircle the urethra they drain only through openings on the urethral floor. According to MacKinsie and Beck, true periurethral tubular epithelial structures appear in the anterior two-thirds of the urethra adjacent to the compound racemose glands of Skene. These, they feel, are distinct from Skene's ducts, are not always present, and are less frequent in the middle third of the urethra. Cabot and Shoemaker,²³ after studying a number of female urethras cut in longitudinal section, came to the conclusion that there are no important gland structures in the proximal two-thirds of the female urethra, and that glands of the female urethra—except Skene's glands—do not play an important role in infections of the female urinary tract. These authors observed

a number of very deep crypts in the urethral mucosa which, running for some distance, might be mistaken for glandular structures if care was not exercised in examining the arrangement of the cells; they state, however, that careful study will show that these crypts are not glands but simply invaginations of the mucosa. Cabot and Shoemaker further described cysts and cell nests in the mucosa and submucosa of the urethra which they believed were derived from von Brunn's cell rests; they did not believe these structures were of notable clinical significance.

The embryologic development of the glandlike tubules about the female urethra has been described by Phallin, Wyatt, Johnson, and me. The *analgen* of these glands arise for the most part entirely above the müllerian tubercle and first appear in the 50 mm. fetus as solid buds protruding from the ventral and lateral sides of the urethra. Branched glands are present in the 128 mm. fetus. Embryologically they are homologous with that portion of the prostate which is cephalad to the prostatic utricle. From the material previously reported,²⁴ it appears that the larger paraurethral ducts and their glands arise from *analgen* above the Müllerian tubercle, that they are identical with the other urethral glands in origin and structure, and that they, like the other tubules emptying into the urethra, are homologous with that portion of the prostate which develops above the union of the mesonephric ducts with the urogenital sinus.

The material for this study was obtained from eleven necropsies. From each a mass of tissue was excised which contained the entire urethra and the surrounding structures lying beneath the pubic arch, the lower portion of the bladder, and the anterior vaginal wall. After fixation each mass was cut to a size suitable for histologic preparation. When so trimmed, each block consisted of the urethra, the periurethral tissues, and the intact suburethral vaginal mucosa. These blocks were then cut transversely into several serial blocks and, subsequently, each block was serially sectioned at 10 micra. Every twenty-fifth section was stained with hematoxylin and eosin. When wax models were to be made these sections were placed under a projecting microscope and enlarged. The enlarged images were transferred onto paper, the outlines of the desired structures were traced, and they were transferred from the paper onto wax plates whose thickness was such as to maintain correct longitudinal proportions. The serial wax plates were subsequently annealed to form models.

Fig. 1.—Drawing of wax model (Model I) of an adult human female urethra with its paraurethral ducts and glands as seen in right lateral view. This reconstruction is in reality a cast of the urethral canal with its outpouching ducts and glandular pockets. The base of the model labelled "Vaginal canal" represents a cast of that portion of the vagina which is beneath and parallel to the urethra. The smaller diagrams demonstrate transverse sections through the urethra, the paraurethral ducts and glands, and the vaginal canal beneath the urethra at different levels above the meatus. Tissues from which this model was reconstructed were obtained at necropsy of a 20-year-old virgin. This model represents the distal 2.4 cm. of a urethra which had a total length of 2.8 cm. It will be noted that no paraurethral ducts open at or immediately within the urethral meatus. Thirty-one ducts empty into this urethra. Although most of these ducts empty into the distal third of the urethra (Fig. 2), several others empty into the middle and proximal thirds. After leaving the urethra the ducts turn cephalad and extend parallel with the urethral canal. One large duct on the right develops into a cyst of considerable size. At the midpoint in the urethra many ducts and glands extend laterally far from the canal; at a more proximal level the urethra is surrounded by many small tubules, and on the right it is encompassed by a thin compact semi-circular sheet of ducts and glands (See Fig. 6).



Fig. 1.—(For legend see opposite page.)

During vaginal examinations ductlike openings just outside and dorsal to the urethral meatus are frequently noted. Occasionally these are the mouths of minor vestibular glands; more often they are entrances of paraurethral ducts. They are usually seen in multiparas, and their location may result from distortion which was a concomitant of labor and which produced a flattening of the urethral eminence with eversion of the distal urethral mucosa. In women who have not borne children, the urethral labia are ordinarily well formed, the urethral mucosa is not everted, and the openings of the paraurethral ducts are usually not visible until the urethral labia are separated and the outermost mucosa exposed.

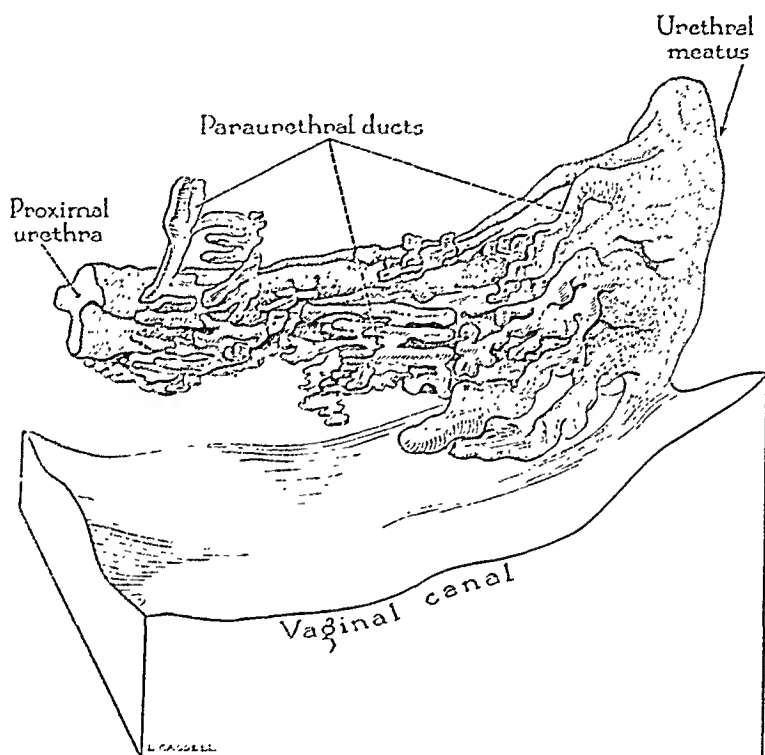


Fig. 2.—Drawing of a wax model (Model II) of an adult human female urethra with its paraurethral ducts and glands as seen in right lateral view. This reconstruction is in reality a cast of the urethral canal with its outpouching ducts and glandular pockets. That portion of the model labelled "Vaginal canal" represents a cast of the vagina beneath and parallel to the urethra. Tissue from which this model was reconstructed was obtained at necropsy of a 38-year-old nullipara. This model represents the distal 2.8 cm. of a urethra measuring 3.0 cm. in total length. No ducts opened at the meatal margins. In this specimen most of the ten larger paraurethral ducts empty into the distal centimeter of the urethra through the lateral and dorsal walls. (See Fig. 3.) Occasional ducts empty also into the most distal portion of the middle third of the urethra. Most of the ducts and glands are noted in the lateral and dorsal periurethral tissues. About the middle third of the urethra, the paraurethral ducts and glands are found far from the urethral canal and, as in Model I (Fig. 1) form semicircular sheets about both the right and left sides of the urethra.

Study of serial sections from all specimens and examination of reconstructions of three urethras (Figs. 1, 2, and 4) reveal certain characteristics that are common to all. In each of them the urethra immediately within the meatus is slitlike with the long axis lying ventrodorsally. The most distal paraurethral ducts open into the canal just within the meatus and extend outward from the urethral mucosa into the dense connective tissue which makes up the urethral wall. This wall is surrounded by and is an integral part of the dense connective

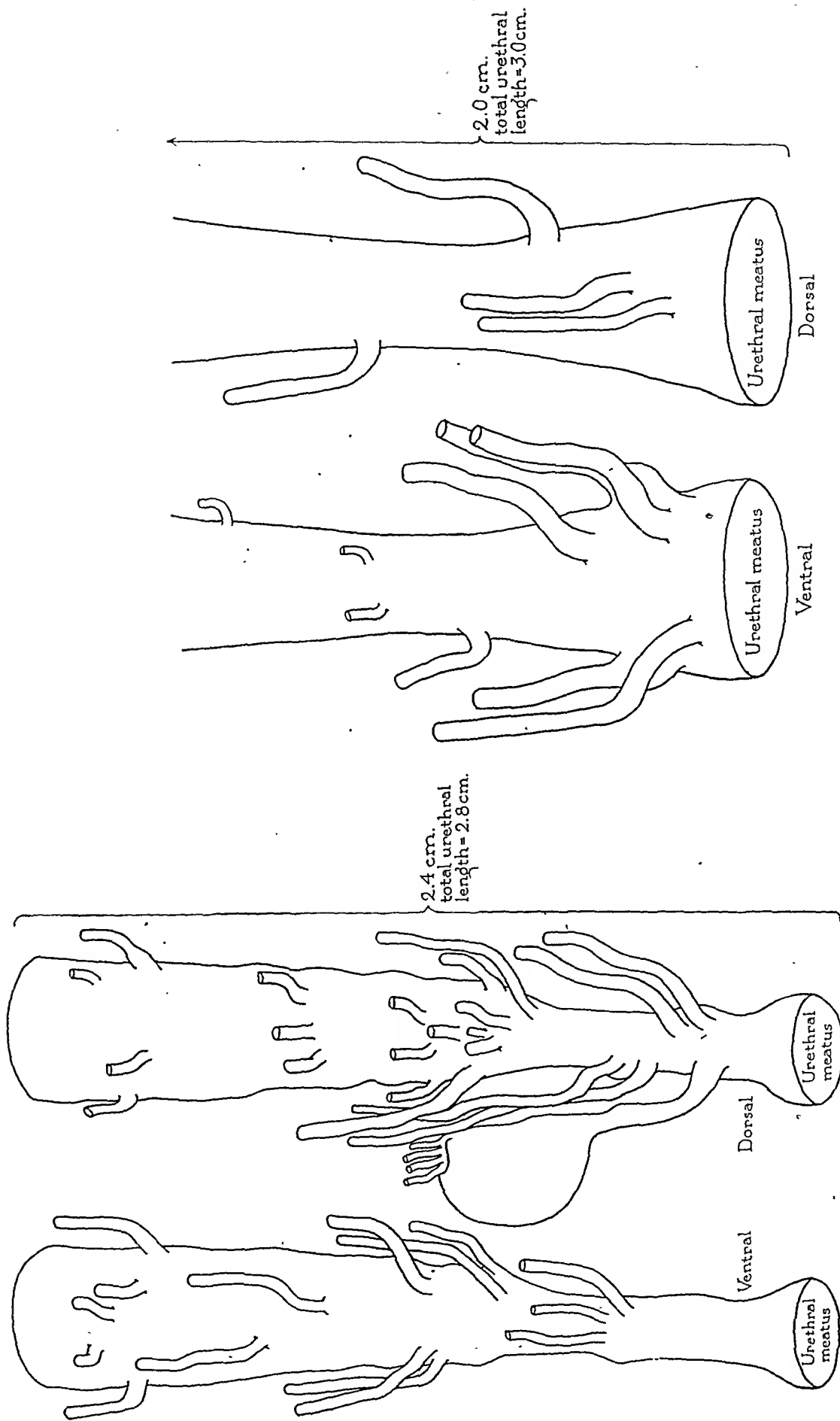


Fig. 3.—Diagrams of Models I and II as viewed dorsally and ventrally to demonstrate the distribution of the paraurethral ducts. The terminal portions of the ducts and the glands are not shown. It will be noted that most of the ducts empty into the distal one-third of the urethra through the dorsolateral and ventrolateral walls.

tissue shelf (the urogenital diaphragm) lying beneath the vaginal mucosa. Infections in the larger of these most distal paraurethral tubules first attracted Skene's attention and led him to describe the structures which have since borne his name.

In all specimens the greatest number of paraurethral ducts empty into the distal one-third of the urethral canal. (In two all duct orifices are in the distal centimeter of the urethral canal; in six the duct openings are limited to the distal 1.5 cm., with most of them near the meatus; in three specimens occasional

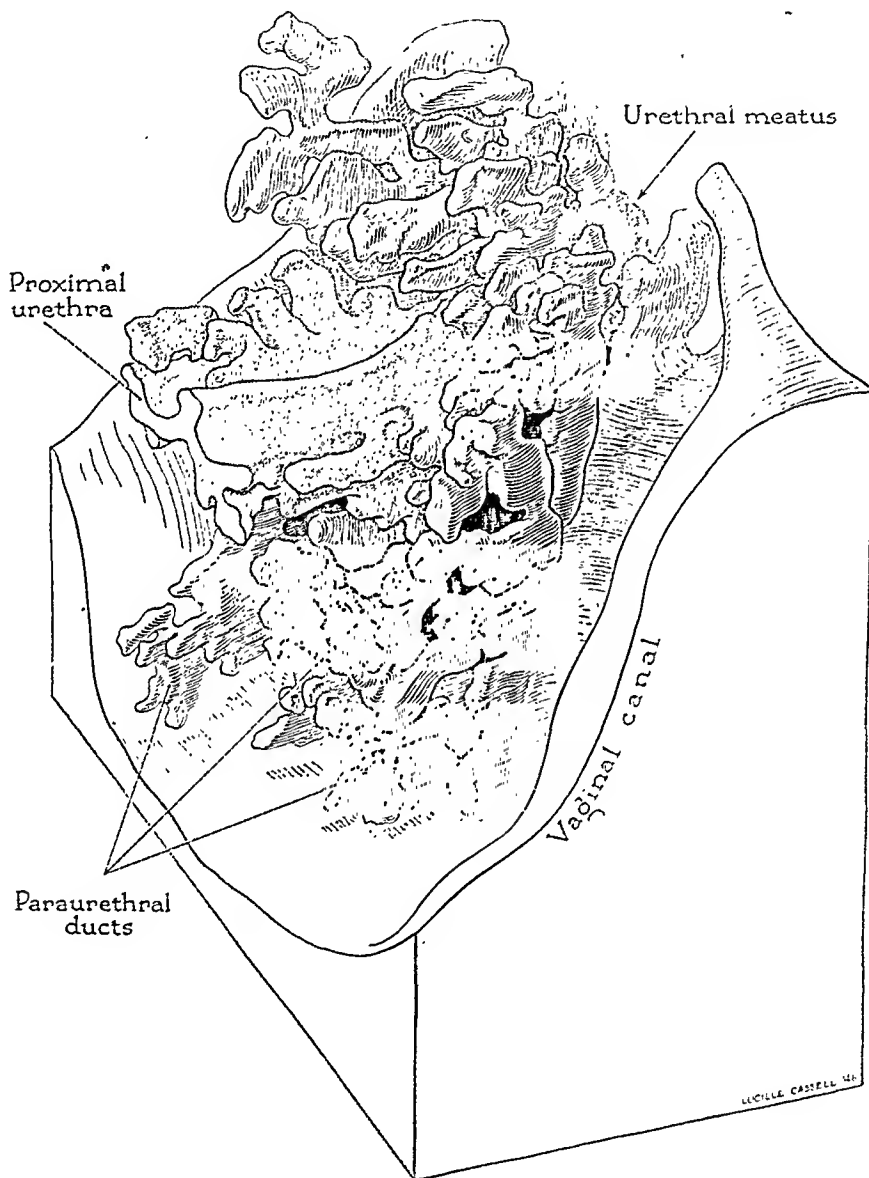


Fig. 4.—Drawing of a wax model (Model III) of an adult human female urethra with its paraurethral ducts and glands as viewed ventrolaterally from the right side. This reconstruction is in reality as cast of the urethral canal with its outpouching ducts and glandular pockets. That part of the model labelled "Vaginal canal" represents a cast of the vagina beneath the urethra and parallel to it. This model is a reconstruction of tissue which was obtained at necropsy of a 32-year-old virgin; it represents the distal 0.8 cm. of a urethra measuring 3.4 cm. in total length. No ducts or glands of appreciable size were found above the level shown in this specimen. No ducts empty outside of the meatus, and none of the ducts measure more than 4 cm. in length. Twenty separate ducts can be identified; these are arranged in four major groups of which two groups empty into the dorsolateral, and two groups into the ventrolateral urethra immediately within the meatus. At the terminations of these tubules there is a marked proliferation of glandular tissue which surrounds the urethra on all sides.

tubules open into the urethral canals throughout most of their lengths) (Fig. 3). There is a definite tendency for the mouths of the ducts to be in four groups (Fig. 4) with two groups on each side, i.e., on each side there is a ventrolateral group and a dorsolateral group. When larger tubules are present they are usually in the dorsolateral location. In addition to these major groups there is, however, a considerable number of ducts opening into the lateral, the dorsal, and a few in the ventral urethral walls. After leaving the urethral canal these tubules turn cephalad and promptly divide into small branches (Fig. 5). These small branches wander outward in the lamina propria away from the urethral canal; they tend to pursue a course somewhat parallel with the urethra itself, and often extend cephalad for a considerable distance. It is not unusual for a single specimen to have a number of these ducts each of which with its branches and glands has an over-all length of from 0.7 to 1.2 centimeters.



Fig. 5.—Photomicrograph of a transverse section through the urethra just within the meatus (Model III) showing the urethra surrounded by many paraurethral tubules and glands. The intact vaginal mucosa borders the lower edge of the section.

More deeply within the urethra the number of paraurethral ducts opening into the urethral canal becomes less. However, in the more cephalic sections the dissemination of ducts, terminal tubules, and glands away from the urethral canal and into the urethral wall is greater. At these levels the smaller branches of the larger ducts which have emptied into the more distal urethra terminate in multiple small budlike out-pocketings and tubular glands. These terminal structures are noted for the most part in the lateral and inferior urethral walls, but each specimen shows a considerable number of ducts and small tubules spreading ventrolaterally and ventral to the urethral canal. This collection of ducts and glands forms a labyrinthlike mass dorsally and laterally which, when indurated by inflammation, produces the thickening so commonly felt after urethral infections.

In some specimens at higher levels the urethra is surrounded on all sides by many small tubular buds and glands which extend to the outermost limits of the connective tissue core making up the urethra itself. Dorsally, they may closely approach the vaginal mucosa. Lateralward, far from the meatus, at the cephalic end of the gland mass, and well away from the urethral canal, the terminal tubules and terminal glands frequently form thin semicircular masses which lie in the lines of stratification of the fibers of connective tissue encircling the urethra (Fig. 6).

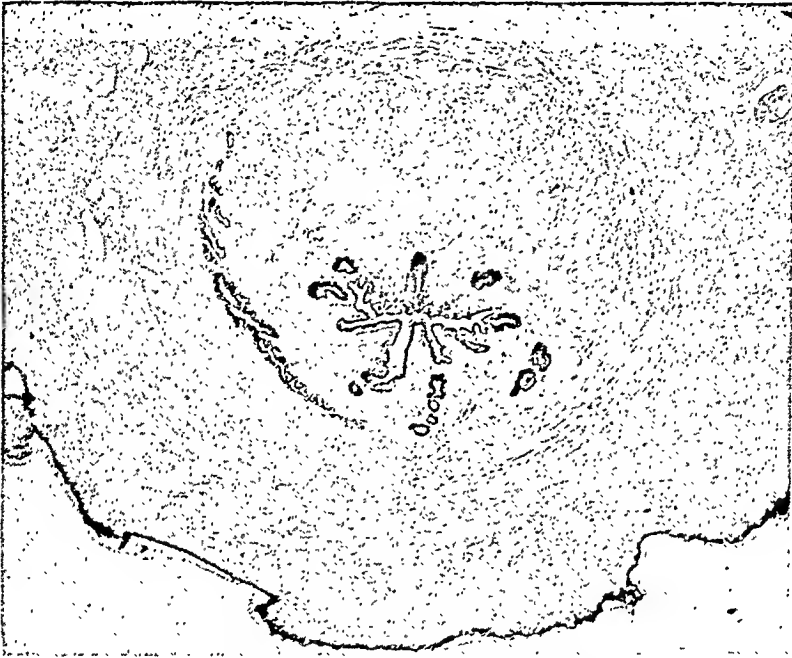


Fig. 6.—Photomicrograph of a transverse section through the urethra and periurethral tissues (Model I) to demonstrate the widespread of paraurethral ducts and glands away from the urethra. In this section (approximately 2.1 cm. proximal to the meatus and 0.5 cm. from the bladder) the paraurethral structures form a thin semicircular mass lying in the fibers forming the urethral wall. The intact vaginal mucosa borders the lower edge of the section.

In the material studied the presence of two large lateral ducts as described by Skene was the exception rather than the rule, and the widespread branching of the terminal divisions was more marked than Skene described. In but two of eleven specimens could two larger tubules, one on each side of the urethra, be followed for any distance. Except for their greater diameter and longer length, these tubules resembled the other paraurethral ducts seen in the same specimen and in other specimens; they were lined by the same type of epithelium and terminated in tubular glands just as the other ducts described herewith. The least number of ducts found in any of the urethras examined was six, the most thirty-one.

Paraurethral glands have, in the past, occasionally been referred to as compound racemose or racemose structures. According to commonly accepted terminology "compound racemose" implies a number of branching ducts with numerous acini grouped about the termination of each duct, as in the major vestibular and parotid glands. The architectural pattern of the paraurethral

glands does not correspond with this description. They are branched tubular glands (Fig. 7), with straight or slightly curved branches, which empty into the paraurethral ducts. They are lined for the most part by columnar epithelium which is made up of cells varying from low columnar, approaching cuboidal,

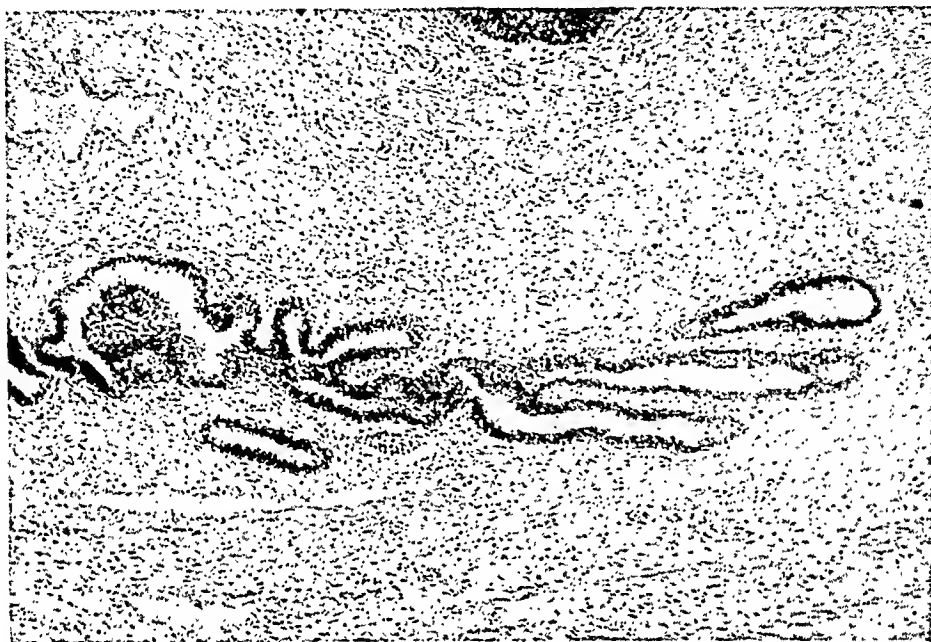


Fig. 7.—Photomicrograph. The paraurethral ducts terminate in branched tubular glands and arborescent tubular pockets.

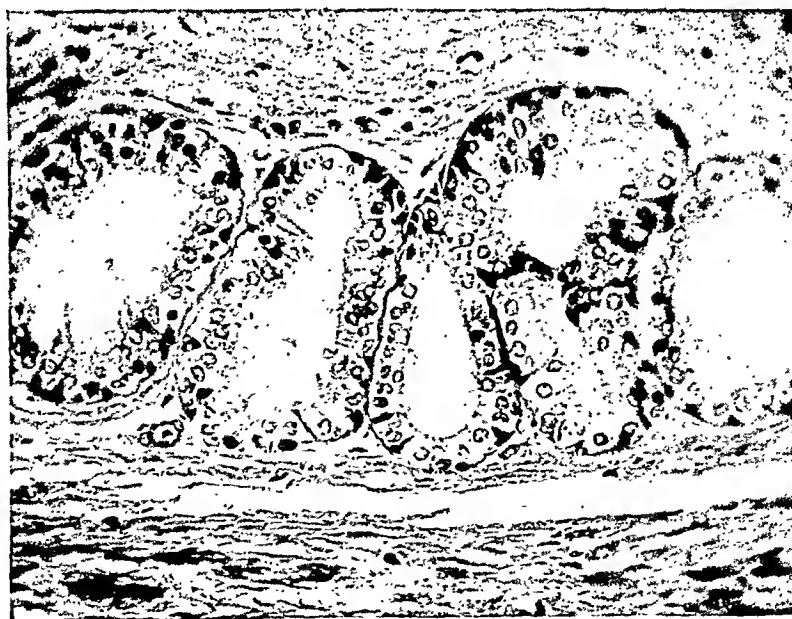


Fig. 8.—Photomicrograph. The tubular paraurethral glands are lined by low columnar epithelium with pale staining cytoplasm and have large centrally or basally placed round nuclei; some but not all of these cells take a mucicarmine stain.

to moderately tall cylindrical cells (Fig. 8). There are occasional nests of mucous secreting cells within this columnar epithelium. These cell nests have a definite secretory activity as demonstrated by mucicarmine stain. Not all

branches of the ducts, however, terminate in glands; many end in small pockets, tiny dilated cystic spaces, and minute arborescent tubules which are lined by a pseudostratified columnar epithelium several times thicker than the lumen of the tubule itself. Infrequent intraepithelial glands of mucous secreting cells are found within this epithelium (Fig. 9).

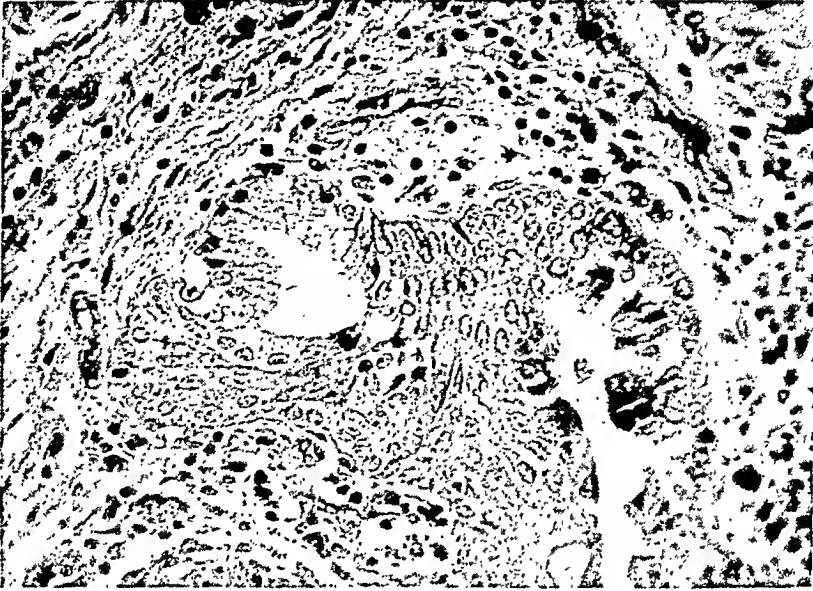


Fig. 9.—Photomicrograph. Infrequent intraepithelial glands of mucous secreting cells are found in the walls of the paraurethral ducts. They take a mucicarmine stain.



Fig. 10.—Photomicrograph of a section in which a small paraurethral duct empties into the urethra. The duct near the urethra is lined by squamous epithelium; more deeply the lining is pseudostratified columnar epithelium.

Most of the smaller and many of the larger branches of the paraurethral ducts are also lined by pseudostratified or true stratified columnar epithelium (Fig. 10). Near their orifices the lining of the ducts becomes the same type as

that of the urethra at that level, i.e., stratified squamous epithelium lines the ducts which empty nearest the meatus; the ducts which open into the midurethra are lined by transitional epithelium which frequently also comprises the urethral mucosa at that level.

Cystic dilatation of the ducts is apparently common, as it was seen in several specimens; these dilatations occurred most often in the terminal portions of the tubular branches. One such cyst was larger than the adjacent urethra. These cysts are lined by thinned out, flattened epithelium of the same type as that of the duct. Some contain an amorphous material which does not take a mucicarmine stain. Inflammatory reactions in and about the ducts and glands is common. Round cell and leucocytic infiltration has been observed beneath the epithelium, and minute localized abscesses and inflammatory destruction of the duct wall has been noted in several instances.

Comment

The definition of the *ductus paraurethrales* in the Basle anatomic nomenclature is "the ducts of Skene's (paraurethral) glands, opening in the vestibule of the vagina on either side of the urethral orifice."²⁵ The definition of the *glandula paraurethralis* as adopted by the Committee on Nomenclature of the German Anatomical Society is "one of a number of mucous glands (Skene's glands) in the wall of the female urethra." The term "perinrethral" glands has also been frequently used for the same structures, although the term is not found in standard medical dictionaries.

The structures as described here are neither *paraurethral* (para-meaning "near, alongside of, a departure from the normal") nor are they *periurethral* (peri-meaning "around or about"). They lie not only alongside and near the urethra, but they are also about and around it, and they empty into it.

The name *prostate muliebris* is present in the dictionaries where it is used as a definitive term for "spongy tissue at the orifice of the meatus urinarius in the female." On the basis of the homology it might be used anatomically for these ducts and glands. Historically de Graaf, Astruc, and Virchow used this descriptive term; more recently it has been suggested again by Korenchevsky.²⁶

Time, custom, and well-deserved recognition for outstanding clinical investigation have associated Alexander Skene's name with the paraurethral ducts. It is fitting that it should be perpetuated; however, it would appear proper to enlarge Skene's description to include the many other large ducts and their glands which are present in most individuals and which are identical with the two which he described.

The most striking finding in this study was the great extent of the tubules and epithelial lined pockets which lie about the adult human female urethra. It is correct to assume that the majority of us have considered this homologue of the prostate to be at best a scattering of insignificant tubules or evaginations on the floor of the urethra with two or occasionally three major ducts opening at the urethral orifice and extending laterally and dorsally in the urethral walls. Instead, the prostatic homologue is most often a widespread branching of ductal channels and glands surrounding the female urethra to some extent on all sides,

hypertension was not present at any time. In the two weeks preceding admission to our care, the patient experienced some ten episodes of fairly severe epistaxis, lasting for from thirty to sixty minutes. No history of arthritis, erythema marginatum, subcutaneous nodules, pleurisy, sunlight intolerance, or headache was given.

The patient had scarlet fever at the age of 13 years and following this had chorea which lasted for four months. She did not have arthritis and was not told of any cardiac complication. Two weeks after recovering from the chorea, the patient had "brain fever" with paralysis of her right arm and leg which lasted only a few days. She was unconscious for this period and her parents "despaired of her life." The present episode of chorea was the first since the childhood attack. The family history was nonecontributory.

On admission to the hospital, the patient was unable to stand, to feed herself, or to talk intelligibly. The temperature was 98.0° F.; the pulse rate, 76 beats per minute; the respiratory rate, 20; and the blood pressure, 116/54. The patient appeared to be dehydrated and evidence of loss of weight was observed. The patient had lost 40 pounds (18.1 kg.) after she became pregnant. The choreiform movements were noted and thought to be of grade 2 intensity (on a basis of 1 to 4 in which 1 represents the least and 4 the greatest intensity). Scattered, nonelevated, erythematous blotches, 2 to 3 cm. in diameter, were observed on the cheeks, arms, and legs.

Results of examination of the optical fields and fundi were negative. Evidence of previous choroiditis was noted. Negative results were obtained on neurologic examination. It was impossible to perform the Romberg test and gait was not observed.

Slight cardiac enlargement, absence of thrills, and regularity of rhythm were noted. Presystolic and systolic murmurs were noted at the apex and a diastolic murmur was noted to the left of the sternum in the third interspace. No evidence of decompensation was discernible.

The size of the uterus suggested a gestation of five months. The fetus was active and the fetal heart, audible. An additional history of slight vaginal bleeding two weeks before admission was obtained.

Results of laboratory studies are given in Table I.

The diagnoses were chorea gravidarum, hyperemesis gravidarum, active rheumatic fever, chronic rheumatic endocarditis with aortic insufficiency, and mitral stenosis and insufficiency.

While the patient was in the hospital, the respiratory rate was never more than 20, the pulse rate never more than 80, and the temperature was never above 98.6° F. except on the day of admission when it was 99.6° F. The blood pressure was 116/54 on admission of the patient, and subsequent determinations were approximately the same. The patient was hospitalized for nineteen days.

The treatment offered was essentially supportive: 2,000 to 3,000 c.c. of a solution of dextrose (1 liter only containing saline) was given intravenously daily for five days with 100 mg. of ascorbic acid (vitamin C), 50 mg. of pyridoxine (vitamin B₆), and 1 ampule of additional supplementary vitamin B added to the fluid. A minimum of visitors was allowed to see the patient. The room was darkened and kept quiet. Two grains (0.13 Gm.) of phenobarbital sodium was given hypodermically twice a day and 1½ grains (0.1 Gm.) of phenobarbital was given by mouth twice a day. Later Nembutal (pentobarbital sodium) and belladonna capsules were given.

Mengert²⁶ mentioned an insidious onset, a course of from eight to ten weeks, with recovery the rule. He suggested rest in bed, quiet, seclusion, good hygiene, and sedatives, such as phenobarbital, paraldehyde, and choral hydrate, when the movements become too severe.

Previous editions of DeLee's¹⁰ text stated that incontinence of urine and feces is a bad omen and that jaundice is regarded similarly. He gave the duration of chorea gravidarum to be from eight days to eight months. The fact that the offspring might be choreic was pointed out. It was stated that permanent mental disturbances in the mother may follow. In a discussion of treatment, isolation in a dark, quiet room, the giving of a vegetable and fruit diet (rich in vitamins, especially B) and abundant fluid was suggested. The physician was urged against temporizing. When hypocalcemia occurs, administration of calcium gluconate and vitamin D was recommended. Treatment with normal pregnancy serum should be tried. It was advised that pregnancy be terminated when general health has begun to suffer, certainly long before incontinence, jaundice, fever, or delirium begins.

Many of these contentions and suggestions are absent from the most recent edition which lists maternal mortality rate varying from 6 to 36 per cent and fetal mortality rate from 50 to 70 per cent. The prophylaxis of chorea gravidarum consists of proper prenatal care. The treatment consists of keeping the patient at rest in bed and administration of sedatives. Emptying of the uterus should be considered if the patient's condition becomes progressively worse. Local anesthesia should be used whenever possible and a neurologist always should be consulted.

Report of Five Cases

From 1922 to 1947, 12,776 confinements were conducted in the obstetric department of St. Marys Hospital. No case of chorea gravidarum was observed. Five cases, however, have been studied at the Mayo Clinic. One of the patients was hospitalized and was treated by us on the emergency gynecology service. The first case to be presented was encountered by us and the remaining four cases were studied by means of clinic records and follow-up letters. None of the patients was delivered at the clinic.

CASE 1.—A 19-year-old married primigravida was admitted to the clinic and was hospitalized on March 27, 1946. She complained of irregular and uncontrolled generalized movements, persistent vomiting, and loss of weight. The patient had married in September, 1945, and she first missed a menstrual period in November, 1945. She had an irregular three-day period of heavy flow at the midinterval between the September and October periods and a physician elsewhere had entertained a diagnosis of "inflamed ovaries." The diagnosis of pregnancy was presumed with the onset of amenorrhea for the menses had always been regular. Nausea and vomiting began the first part of December and continued until admission. Sore breasts and urinary frequency were noted in January, 1946. Three weeks before admission, the patient experienced some vague, cramplike pains in the lower part of the abdomen which lasted for from a few seconds to several minutes. She was thought to be aborting. At that time she was vomiting on the average of four times per day. Ten days before admission, choreiform movements were noted. The patient first noted some blurring of vision and an inability to hold and manipulate objects with precision. She "wiggled in her chair" and was called "hysterical" by her father. She had no convulsions. She had been admitted to a hospital elsewhere for study and the presumptive diagnosis was toxemia of pregnancy. Edema, albuminuria, or

The patient was delivered of a normal female infant weighing 5 pounds (2.3 kg.) by her local physician on July 8, 1946. The postpartum period was uneventful for both mother and infant.

CASE 2.—A 25-year-old woman, gravida iii, para ii, registered at the clinic July 20, 1925, in the fifth month of pregnancy. Her chief complaint was of choreiform movements. Study of the family history revealed that the father had died of diabetes and one brother had "sick headaches." The patient had had influenza, scarlet fever, and tonsillitis as a child. She had had rheumatic fever seven years before admission and chorea six years before admission and had undergone tonsillectomy five and a half years before admission. The patient had had headaches since the age of 12 years, had blurred vision at times, and had diminished hearing with tinnitus on the right side. The menses had always been normal. The patient had worked as a seamstress from the age of 18 years and enjoyed her work except that when she was very busy she became extremely nervous. Her mother became ill seven years before the patient came to the clinic and the patient carried on the work of sewing for both of them. She suffered a "nervous breakdown" and had "exaggerated choreiform" movements the first time for two and a half weeks and it was necessary for her to stay in bed. She recovered slowly and underwent tonsillectomy during her convalescence. She married because she was told that marriage and pregnancy would improve her nervous condition and that if she did not marry she would probably become worse.

Four years before admission, after three months of marriage, she became pregnant and began to have choreiform movements so severely that she could not hold things in her hands or speak. Associated symptoms were blurring of vision, a "sickening feeling in the bones" of her arms and legs—akin to weakness and numbness—and pain in the back. The chorea subsided in the fifth month of gestation after one month of hospitalization and the remainder of the pregnancy was uneventful.

She suffered chorea in the first half of the second pregnancy, one and a half years before admission, with the same associated symptoms, which cleared in the second half of the pregnancy. She was then well and had never felt better until five months before admission when she became pregnant again and the chorea returned.

On admission she was unable to keep her arms or her legs still and was described as being very fidgety. The speech was not articulate and facial grimacing was present. She suffered some shortness of breath and felt as though the movements of her chest were restricted. Additional complaints were of urinary frequency, nocturia, back pain, and loss of 11 pounds (5.0 kg.).

On physical examination the temperature was 99.4° F.; pulse rate, 96; and blood pressure, 140/85. The teeth were in poor condition. Examination of the heart revealed a faint, diastolic murmur at the base. The size of the uterus was consistent with a five-month gestation.

Examination of a noncatheterized urine specimen revealed albuminuria, grade 2 plus, and pyuria, grade 1 plus. Erythrocyte count was 3,560,000 and leucocyte count, 9,300 per cubic millimeter, and the concentration of hemoglobin was 56 per cent. The color index was 0.7 plus. Differential count revealed the following: 78 per cent polymorphonuclear neutrophilic leucocytes, 16.5 per cent lymphocytes, 3.5 per cent eosinophiles; moderate anisocytosis, slight poikilocytosis and polychromatophilia. Wassermann test gave negative results.

No abnormalities were found during examination of the eyes, ears, nose, and throat. Neurologic examination gave negative results. In psychiatric interview, the patient confided that coitus had never been pleasurable.

TABLE I. LABORATORY STUDIES OF CASE 1

	RESULTS
Urine	Specific gravity: 1.005 to 1.017
	Alkaline
	No sugar, albumin, acetone, or diacetic acid
	Occasional pus cells in uncatheterized specimen
Blood	Hemoglobin: 13.6 and 12.2 Gm. per 100 c.c.
	Erythrocytes: 4,280,000; 4,090,000 per cubic millimeter
	Leucocytes: March 28, 9,500; March 30, 6,300; April 4, 7,300; May 6, 12,400 (two readings) per cubic millimeter
	Differential count: 43 per cent, immature polymorphonuclear leucocytes; 40 per cent mature forms; 12 per cent lymphocytes; 5 per cent monocytes
	Urea: 22 mg. per 100 c.c.
	Chlorides: 583 mg. per 100 c.c. of plasma
	Carbon dioxide combining power: 48.5 volumes per 100 c.c. of plasma
	Serum calcium: 9.5 and 8.2 mg. per 100 c.c. on two successive days
	Serum protein: 7.4 mg. per 100 c.c.
	Flocculation test: negative
	Sedimentation rate (Westergren): March 27, 63 mm.; March 30, 51 mm.; April 3, 67 mm.; April 13, 61 mm. in one hour
	Culture (brain broth and blood agar): no growth in 48 hours
Roentgenologic examination	Elevation of the left side of the diaphragm
Electrocardiographic examination	Heart rate, 85; sinus arrhythmia; T ₂ of low amplitude; P ₂ and P ₃

Slight improvement was noted on the third hospital day both in the course of the vomiting and chorea. The patient vomited four times on the first day of hospitalization, three times on the second day, and only once on the third day. By the fifth day definite improvement was observed, and frequent light, dry feedings were offered. On the seventh hospital day, a general diet was allowed and the choreiform movements were then difficult to detect. Pyridoxine was given by mouth for five days thereafter in 50 mg. doses.

Beginning on the twelfth hospital day, 20 grains (1.3 Gm.) of sodium salicylate were administered in enteric-coated tablets three times a day and 4 mg. of vitamin K was given each day. Supplementary vitamins, especially those of the B complex and iron were taken by the patient. She was discharged on the nineteenth hospital day and was advised to return at intervals.

She returned on May 6, 1946, feeling well. The sedimentation rate was 54 mm. (Westergren). The pulse rate both at rest and after exercise was elevated only slightly. Administration of the salicylates was continued. On June 3, 1946, all medication except iron and vitamin supplements was discontinued. The patient felt well. The sedimentation rate was still elevated (62 mm.). On June 15, when the patient was examined elsewhere, albuminuria was graded 1+ and the ankles were slightly swollen. The albuminuria and swelling subsided when she stayed in bed for a few days. Determination of the concentration of salicylates in the blood was carried out on three occasions during our observation of this patient. The results were: April 10, 1946, 10.4 mg.; May 6, 1946, 20.2 mg.; June 3, 1946, 4.2 mg. per 100 c.c.

CASE 4.—A married unipara, 21 years old, gravida ii, para i, was studied at the clinic in August, 1940, in the fifth month of pregnancy. Her chief complaint was of nervousness. The family history was of no particular significance except for the information that the patient's mother and aunt had both been extremely nervous during their pregnancies but not to the extent that the patient was. Study of the past history showed that the patient had had rheumatic fever at the age of 9 years and mild scarlet fever associated with migratory polyarthritis of six weeks' duration at the age of 18 years. The menstrual history was normal. In September of the preceding year, after two years of marriage, the patient had had a full-term pregnancy and after a long labor was delivered of an infant who weighed 9 pounds (4.1 kg.). She had been discharged from the hospital in seven days.

The patient had apparently been normal until January, 1940. At that time, rheumatic fever developed and she was in bed for a month. Following this episode, she failed to gain strength and lacked ambition. In March, the patient's speech began to become thick and slow and this condition progressed until the middle of June when she could hardly speak at all. The last menstrual period began March 28, 1940. About that time, she had begun to note uncoordinated movements of the head and extremities. She did not "feel nervous." She was hospitalized elsewhere from June 21 to 29, without improvement. She was studied by several physicians and by an osteopath. Treatment had consisted of injections of liver extract. Shortly before the patient's admission, painful areas on the legs and a sore mouth developed. The lesions on the legs appeared in crops. She had noted a tendency to easy bruising. Members of the Department of Neurology obtained some additional information. It was noted that the patient's mother had sick headaches. The patient had had headaches since early girlhood. These had improved after her marriage. The patient had always been emotionally labile.

On physical examination the blood pressure was 100/78, and the pulse rate, 88. The patient was unable to sit still, and movements of the extremities and the head were continuous and purposeless. There was much grimacing. The patient had extreme difficulty in walking, talking, and swallowing. Nystagmus was not noted. Hypertrophy of the tonsils was grade 1. Bilateral submaxillary lymphadenopathy was noted. The lungs were normal. No cardiac abnormality was noted. Ears and nose were examined and found to be normal. Reddened, warm, slightly painful, blue, quarter-sized lesions were observed on the legs. On neurologic examination, grimacing, hypotonia, diminished deep reflexes, and adiadokocinesis were observed. Speech impairment and inability to perform fine movements were also noted. The lesions of the skin were thought to be symptomatic of dermatitis medicamentosa as a history of intake of bromides was obtained. A dental examination revealed no foci of infection.

Examination of the blood showed the concentration of hemoglobin to be 11.0 Gm., an erythrocyte count of 4,100,000, and a leucocyte count of 7,400. Differential count showed 66 per cent polymorphonuclear neutrophilic leucocytes, 26 per cent lymphocytes, 7 per cent monocytes, and 1 per cent eosinophiles. The platelet count was 121,000 per cubic millimeter of blood. Flocculation test for syphilis and roentgenologic examination of the thorax and head gave negative results. The coagulation time was five minutes, clot retraction was complete at one hour, and the sedimentation rate was 45 mm. per hour.

The clinical impression was that chorea gravidarum and dermatitis medicamentosa were present. The patient was advised to rest, take sedatives and vitamin supplements, and to stop taking bromides.

The patient was delivered of a normal infant, January, 1941, elsewhere, without further difficulty. Another baby was born in December, 1945; chorea did not recur.

The clinical impression was that chorea gravidarum was present and it was felt that the patient might have low-grade, chronic nephritis on the basis of the albuminuria, elevated systolic blood pressure, and slightly diminished renal function. Routine suggestions for the management of chorea were made. It was advised that renal function be observed carefully for the remainder of the pregnancy. Follow-up letter stated that the patient was delivered of a normal baby without untoward incident.

CASE 3.—A 23-year-old married multipara, gravida iv, para iii, reported to the clinic in March, 1931, in what was thought to be the seventh month of pregnancy. She was referred to the clinic with a tentative diagnosis of brain tumor. One brother had committed suicide. The patient had had scarlet fever, influenza, and tonsillitis as a child. She underwent tonsillectomy at the age of 10 years. The menses had always been normal but the patient always suffered dizziness at the time of her menstrual periods.

Four months before admission, in the third month of pregnancy, the patient noted some weakness in her right arm while playing cards and later some weakness in the right leg. She had difficulty in walking. Subsequently, weakness in the right side of the face and difficulty in talking were noticed. Her words seemed "thick and unmanageable." The patient slept poorly, was nervous, and had much more difficulty when she was being watched. Slight anorexia was present.

In the course of the neurologic examination the patient told that she had had slight tinnitus for fourteen years and complete deafness of the left ear. In the two months preceding admission, the patient had noted slurring of her speech and attacks of dizziness. She had had blurring of vision for one month. It was discovered that the weakness and incoordination of the right arm came on overnight after she saw her mother who was quite ill. The patient was irritable and cried frequently without provocation. She complained that her tongue felt too big for her mouth. She admitted that she worried considerably over her health and that she and her husband had many financial worries. She had been unable to do any work for one month.

Physical examination showed the temperature to be 98.0° F.; the pulse rate, 76; and the blood pressure, 122/70. Obesity, slight pallor, and a seven-month gestation were noted. The patient talked out of the left side of her mouth. Slight facial palsy was observed and was considered to be more apparent than real. She had great difficulty in talking and articulated poorly. Slight horizontal nystagmus was present. The teeth were in fair condition. The abdominal reflexes were absent. Coarse, jerky, uncoordinated, purposeless movements, more marked on the right side, were described by the examiner.

Examination of the heart and lung revealed no abnormalities. Examination of the eyes, including fields and fundi, gave negative results. Active gingivitis was noted in the course of dental examination.

Laboratory examination of a noncatheterized specimen of urine showed albuminuria, grade 2 plus, pyuria, grade 1, and a slight trace of sugar. The erythrocyte count was 4,250,000 and leucocyte count, 9,500 per cubic millimeter, and the concentration of hemoglobin, 14.7 Gm. per 100 c.c. Result of the flocculation test for syphilis was negative. Roentgenograms of the head and thorax did not show any abnormalities.

A diagnosis of chorea gravidarum was made after a diagnosis of early multiple sclerosis had been excluded.

The patient subsequently gave birth to normal twins (a male, 6 pounds [2.7 kg.], and a female, 7 pounds [3.2 kg.]). Two years after this twin pregnancy, the patient gave birth to a normal female child. During this last pregnancy, chorea did not recur. Both deliveries were without untoward event.

TABLE II. SUMMARY OF FINDINGS IN

CASE	AGE	MARITAL STATUS	OBSTETRIC STATUS		HISTORY OF CHOREA		HISTORY OF RHEUMATIC FEVER OR SCARLET FEVER	HEART DISEASE	EVIDENCE OF TOXEMIA
			GRAVIDA	PARA	ASSOCIATED WITH PREGNANCY	UNASSOCIATED WITH PREGNANCY			
1	19	Married	i	0	0	1	Scarlet fever	Present	None
2	25	Married	iii	ii	2	1	Scarlet fever, rheumatic fever	Probably present	B.P. 140/85. Albuminuria, grade 2 and pyuria
3	23	Married	iv	iii	0	0	Scarlet fever	Not present	None
4	21	Married	ii	i	0	0	Rheumatic fever	Not present	None
5	19	Unmarried	i	0	0	1	None	Present	None

*Routine supportive measures were suggested to these patients.

four and a half months pregnant, chorea became more marked. Thickness of speech and marked insomnia were noted at this time. Sedation with barbiturates and bromides was provided. The most significant improvement in the chorea was noted during the last six weeks of pregnancy. The patient married during the antenatal period; the date was not stated. On July 8, 1946, after a normal labor, a 6 pound (2.7 kg.) infant was delivered by low forceps. Cyclopropane and oxygen anesthesia was used. There was no evidence of chorea in the puerperium. The follow-up examination on Aug. 22, 1946, revealed no evidence of chorea and the patient felt well.

Comment

It is impossible to draw any significant conclusions from this small series of cases. A summary of the findings is given in Table II. The average age of our patients was 21.4 years. Four were married and one was unmarried. Two were primigravidas and three were multigravidas. In all of these cases chorea began in the first half of pregnancy and lasted for periods varying from two and a half weeks to five months. All of the pregnancies were terminated spontaneously at term and six normal babies were born (one twin pregnancy).

Only one patient (in Case 1), whose condition might be described as moderately severe, required hospitalization while under our care. One other patient had been hospitalized elsewhere in the pregnancy under consideration. The therapy offered to our hospitalized patient was by no means specific and was directed essentially toward the relief of the independent or possibly associated

CASE 5.—An unmarried primigravida, 19 years old, registered at the clinic in January, 1946. Her chief complaints were of nervousness and amenorrhea. The patient wondered if the nervousness represented a recurrence of chorea which she previously had had and if the amenorrhea represented pregnancy which she feared. Her family history was noncontributory. The patient had had chorea at the age of 12 years. She was in bed for a period of three months and was unable to walk or talk and suffered with severe generalized twitching movements. She cried a good deal. Tonsillectomy had been performed in 1941. Menstrual periods always had been irregular, occurring at intervals of three to eight weeks. Her last menstrual period had been in September, 1945.

In the middle of October, 1945, the patient began to have morning nausea and vomiting and noted an accentuation of nervousness which had been rather prominent for the preceding two years. At first the nervousness was simply manifested by such things as nail-biting and insomnia. She then noted that she became more easily excitable and easier to anger. Her speech became slurred and in the two months preceding admission she began to notice jerking movement similar to those that she had suffered when she was a child.

On physical examination, the temperature was 98.2° F.; the pulse rate, 66; and the blood pressure, 120/80. The patient recently had lost 3 pounds (1.4 kg.). She was well developed and well nourished, and the physical examination gave completely negative results except for a systolic murmur at the apex and a definite, but soft, presystolic murmur heard when the patient was in the left, lateral recumbent position. On pelvic examination, the cervix was found to be soft and the uterus enlarged to a size consistent with a two-month gestation.

Questioning by the neurologist revealed the following pertinent facts: The mother of the patient was highly emotional and nervous. At the age of 12 years, shortly after the patient injured the lower part of her back, chorea developed. It was determined that the patient intended to marry the alleged father if their religious differences could be settled. On neurologic examination, no nystagmus was noted. The reflexes were normal and slightly more active on the left side. The jerking movements were confined principally to the arms and legs although the face was involved to a considerable extent.

Laboratory study of the urine gave negative results. The concentration of hemoglobin was 13.1 Gm. per 100 c.c. The erythrocyte count was 4,790,000 and the leucocyte count was 7,600. The differential count showed 77.5 per cent polymorphonuclear neutrophilic leucocytes, 15.5 per cent lymphocytes, 4.5 per cent monocytes, 1.5 per cent eosinophiles, and 1 per cent basophiles. The result of the flocculation test for syphilis was negative. Roentgenologic examination of the thorax gave negative results. The electrocardiogram showed a cardiac rate of 72 beats per minute, slight sinus arrhythmia, and slurred QRS I and III. The sedimentation rate was 17 mm. Result of the Friedman test was positive.

The diagnoses were chorea gravidarum and rheumatic endocarditis with mitral stenosis and insufficiency. It was felt that the rheumatic state was in a relatively inactive phase. No great concern was felt concerning the cardiac status as the consulting cardiologist estimated the cardiac reserve to be adequate. A high-protein diet, adequate intake of milk, calcium lactate, and vitamin supplements were advised.

A letter from the attending obstetrician elsewhere after delivery of this patient revealed the following data: She gained 12 pounds (5.4 kg.) during the entire gestation and repeated determinations of the blood pressure, urinalyses, and blood counts gave results within normal limits. When the patient was

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FIVE CASES OF CHOREA GRAVIDARUM

PSYCHO- GENIC "COLOR"	CHOREA				TERMINA- TION OF PREGNANCY	RESULT	SUBSEQUENT PREG- NANCIES
	MONTH OF PREGNANCY AT ONSET	MONTH OF CESSA- TION	DURATION	TREATMENT			
Not present	Approx. fourth	Approx. fifth	Approx. 2½ weeks	Sedatives, vi- tamin ther- apy, salicy- lates	Spontaneous	Infant liv- ing	None
Present	First half of preg- nancy	Approx. fifth	Approx. 6 weeks	None*	Spontaneous	Infant liv- ing	Not known
Present	Third	Eighth (?)	At least 4 months	None*	Spontaneous	Infants liv- ing (twin preg.)	One normal pregnancy without cho- rea
Present	First	Sixth (?)	At least 4 months	None*	Spontaneous	Infant liv- ing	One normal pregnancy without cho- rea
Present	Second	Seventh	Approx. 5 months	None*	Spontaneous (low for- ceps)	Infant liv- ing	None

nausea and vomiting. Both complications were relieved at about the same time. Two recent publications in the South American literature referred to the use of pyridoxine (vitamin B₆) as a therapeutic agent in cases of chorea gravidarum with gratifying results. We used this agent in the treatment of the hyperemesis in this case but also used other measures, so any evaluation of the therapeutic effect of pyridoxine in this condition is impossible.

No evidence to support a toxemic etiology of this condition was present in this series, other than perhaps the nausea and vomiting mentioned in two cases. A rheumatic background was present in all of the cases. A past history of chorea was given in three cases and of rheumatic fever in two cases. Heart disease was present in three cases. In Case 3, a patient who did not give a history of chorea or rheumatic fever and had no evidence of heart disease had had scarlet fever and several episodes of tonsillitis as a child which might be classified as a rheumatic-equivalent type of background. In the terminology of Weigner,⁷ psychogenic "color" was noted in four of the five pregnancies.

Summary

The recent literature concerning chorea gravidarum is considered. Reference is made to the toxemic, allergic, rheumatic, infectious, and psychogenic hypotheses of origin of chorea gravidarum. The current status of authoritative obstetric opinion is reviewed. Five cases of chorea gravidarum observed at the clinic are presented. The case for a rheumatic etiology of this condition is further strengthened by these reports. A suggestion of psychogenic "color" was present in this series. Conservative methods of treatment and delivery were used in all cases. A successful outcome of the pregnancy occurred in all instances.

most notably laterally and posteriorly. The urethra might well be compared to a tree about which and growing outward from its base are numerous stunted branches, the paraurethral ducts and glands.

The marked variation in the extent of the paraurethral ducts in different individuals is also of interest. These structures usually do not surround the urethra in its entire length; commonly they are limited to the outer half. They may, however, extend along the distal two-thirds or more of the urethral canal reaching to within a few millimeters of the bladder. In some individuals they form a labyrinthine mass encircling the urethra on all sides, in others they lie almost wholly laterally and posteriorly.

While discussion concerning the nature of the gland-like tubules about the proximal urethra is not pertinent to this presentation, certain observations are of interest. There are many small glandular elements to be found about the upper one-half of the urethra. They are evident in transverse sections where they are most often seen laterally far from the urethral canal; they are the terminal glands of the ducts which empty into the urethra at a more distal point. Transverse serial sections show that the crypts and lacunae of that portion of the proximal urethra above the large ducts and their glands and near the bladder are lined by the same type of epithelium as that which lines the terminal glands and tubules of the paraurethral ducts. Furthermore, there are areas of infolding or invaginations of the urethral mucosa which are also lined by a similar type of epithelium. It would appear that most of these crypts, lacunae, and invaginations are diminutive developments from the same embryologic source as are the larger structures found more distally. Some of these lacunae have lumina and subdivisions comparable to their larger counterparts. In other words, the proximal urethra has rudimentary glands of exactly the same type as the larger glands found in the distal urethra. There seems every reason to believe that inflammation, irritation, and obstruction may result in the development of cystic enlargements of the intraepithelial glands and small submucosal lacunae of the proximal urethra as MacKinsie and Beck postulated in explaining the cysts which are sometimes found about the upper third of the female urethra.

The role of the paraurethral ducts in gonococcal infections of the female genitals is too well understood to require comment. Dr. Arthur Curtis has pointed out the value of palpating bristlelike thickening of the posterolateral ducts as pathognomonic evidence of a previous gonorrheal infection. That these ducts may be involved in other types of urethritis is less commonly realized. I have seen several women traumatized by catheterization who have subsequently developed a granular urethritis and in whom a marked induration (or periurethritis) of the posterior and lateral periurethral tissues strongly suggested involvement of the paraurethral ducts and glands.

Obstruction of the narrow outlet of infected paraurethral ducts is an important factor in the etiology of abscesses of the anterior vaginal wall. These abscesses may reach considerable size and extend along the fascial planes between the urethra and the vagina. Paraurethral abscesses of small size may also form in the urethral wall itself and eventually rupture into the urethra with the formation of a urethral pocket that ultimately, due to repeated infec-

NEWER OBSTETRIC ANALGESICS*

Preliminary Evaluation of Compounds No. 10720 and No. 10820 (Dolophine)

CURTIS J. LUND, M.S., M.D., NEW ORLEANS, LA.

(From the Department of Obstetrics and Gynecology, University of
Minnesota Medical School)

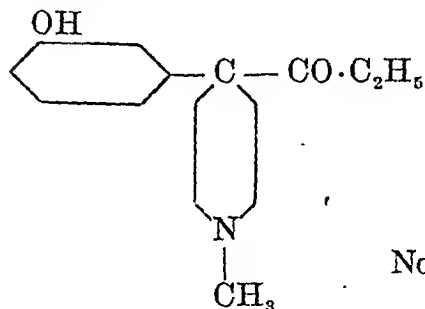
DEMEROL was the first of what appears to be a long line of potent new analgesic agents. Some of these were prepared by German chemists and were acquired by this country during the war. Recently, the U. S. Department of Commerce released information concerning these drugs in report No. 981,¹ which describes compounds No. 10720 and No. 10820, as well as many others which may have clinical value. The purpose of this report is to suggest methods of evaluation of obstetric analgesics and to present results of investigations upon the two mentioned compounds.

Between 1930 and 1940, many new barbiturates were compounded, and nearly every one was highly recommended by someone, as the perfect obstetric analgesic. Yet, today, the champions of those drugs have discarded them in favor of the newer synthetic analgesics, e.g., Demerol. These past experiences must prevent unwarranted enthusiasm by all who share in the development of new analgesics. Nevertheless, it is important that promising new compounds be carefully investigated.

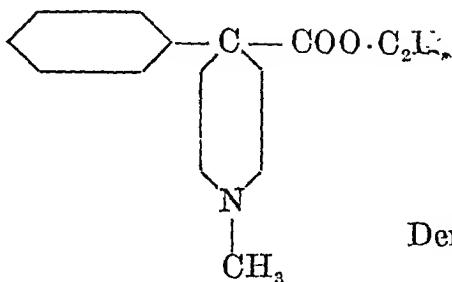
To evaluate any analgesic properly, it is well to consider the qualifications of a perfect obstetric analgesic. Such a drug would give complete analgesia, with complete safety to mother and baby, without interference with the normal processes of labor and delivery. Furthermore, it should be inexpensive, easily administered, and readily used in any environment. Such an agent does not exist, and perhaps never will; yet these are criteria by which all new obstetric analgesic agents should be tried.

Pharmacology

Compound No. 10720 is strikingly similar to Demerol. Instead of having a carboxyl group as does Demerol, it is a ketone. In addition it has an OH added to the benzene ring.



No. 10720



Demerol

*Presented, by invitation, at a meeting of the New Orleans Obstetrical and Gynecological Society, Nov. 6, 1947.

Very little is known concerning the pharmacology of this drug. Only brief reports have appeared in the literature.^{2, 3} These studies indicated that this compound and several similar synthetic analgesics depressed blood pressure, salivation, and the heart rate of experimental animals. The effect on respiration varied—No. 10720 did depress respiration in the rat. The suggested dosage in man was about 7.5 mg.

Dolophine (No. 10820) is only slightly different in structure. It is a diphenyl butanone compound which is being rather widely investigated at present. The suggested dosage of this drug has been from 5 to 10 mg.

Results

The results are based on observations of 50 obstetric patients who received compound No. 10720* and of 18 who received Dolophine (No. 10820)* during labor. Dolophine was used first, but was discarded as inferior when No. 10720 became available.

Material

No attempt was made to select the patients for this study, although it is obvious that some selection is inevitable. For example, analgesics of any kind would not be given to a woman in premature labor, unless complications of pregnancy or labor so demanded. The data will show that even closer adherence to such principles might have produced better results.

Slightly more than half of the patients were "house cases," and the remainder were private patients. There were 30 primiparas and 20 multiparas, most of whom (88 per cent), according to menstrual history, were at term. The remainder were from two to four weeks from term. A third of these mothers had complications of pregnancy, such as toxemia, heart disease, diabetes, iso-immunization, jaundice, previous cesarean section, and the like.

Dosage

Five to ten mg. of compound No. 10720 (hereafter to be called No. 10720) had been tentatively suggested as a possible therapeutic range. The smaller one was chosen, and it proved to be satisfactory. Later, the dose was increased to 7.5 and finally to 10 mg. Although the larger doses were well tolerated by the mother, there were some undesirable fetal effects, which will be discussed later. Administration was by hypodermic.

In nine of the patients, the drug was repeated. As a rule, the succeeding doses were spaced at least four hours apart. (More recently, a patient not included in this report received four successive doses within a twenty-four hour period, with good effect, and without apparent harm to mother or baby.)

Finally, the drug was combined with 1/200 or 1/300 grain of scopolamine. The importance of this combination will be discussed subsequently.

Onset and Duration of Action

By action, we mean the onset of appreciable obstetric analgesia, and it does not refer to maximum analgesia. Only an occasional patient noted subjective relief within fifteen minutes. With very few exceptions, this effect was present within thirty to forty-five minutes after the administration (Table I). This table also shows that the duration of action was as sharply limited as was

*Supplied through the courtesy of Eli Lilly & Co., Indianapolis, Ind.

its onset. Only nineteen patients could be fully observed. The others were delivered while the drug was still effective; so duration could not be determined. No patient had analgesia for more than three and one-half hours, but most patients obtained from two and one-half to three hours of relief.

TABLE I. ONSET AND DURATION OF ANALGESIA

ONSET		DURATION	
15 minutes	2	1½ hours	0
30 minutes	14	2½ hours	6
45 minutes	16	3½ hours	13
60 minutes	4	No data	12
No data	14	Delivery intervened	19
	—	1½ hours	3
	50	2½ hours	14
		3 hours	2
			—
			19
			—
			50

Untoward Effects

These were infrequent. Many mothers noted some dryness of the mouth and some were giddy. Neither of these effects was annoying. Three had nausea and emesis. Perhaps this was from the drug; yet such gastrointestinal disturbances are not uncommon in labor, without medication. One complained of vertigo, as distinguished from the lightheaded, giddy sensation which was common. There were no other subjective complaints.

Such objective measurements as pulse, respiration, blood pressure, and fetal heart rate were recorded before and during treatment. Early in the study, these vital signs were repeatedly observed, but as the study progressed without the appearance of significant changes, we became less exacting. Approximately half (23) of the patients had detailed observation. One patient had a decrease in pulse rate from 70 to 62; another had a slight slowing of respirations; and one other had a drop in blood pressure from 130/80 to 120/70. There were no clearly demonstrable changes in the fetal heart rate due to the drug.

In no patient did we observe excitation produced by the drug. Two of the mothers were wildly excited before No. 10720 was given and this persisted in spite of therapy. On the other hand many mothers had marked relief from their apprehension and were able to sleep and rest between contractions even though analgesia was incomplete.

Analgesic Effects

Under this heading we will consider the three qualities of an obstetric analgesic agent: (1) analgesia, (2) amnesia, and (3) rest.

Analgesia could be studied in 46 patients—the others delivered before effect could take place, i.e., within thirty minutes. Table II lists the results. Of the entire group, about half had satisfactory analgesia (20 per cent excellent and 30 per cent good); the other half had fair analgesia or none at all (40 per cent fair and 10 per cent none).

Of considerable interest was the improvement in analgesia which followed the combination of scopolamine with 5 mg. of No. 10720. In this small group of 13 mothers, 85 per cent had satisfactory analgesia; 15 per cent had partial success, and there were no failures. In one patient, 5 mg. of No. 10720 was combined with 1/200 grain scopolamine. This produced good analgesia. About five hours later, 7.5 mg. of No. 10720 alone was given and this produced

only fair analgesia. In another five hours the first combination was repeated and again good analgesia was produced. Whether this is a synergistic action or not could not be determined from this study. Scott et al.³ did not observe improved analgesia with the addition of scopolamine.

Rest and sleep between uterine contractions frequently followed the use of No. 10720. Nearly 30 per cent had excellent results which meant that the patient slept between contractions. A slightly greater number (37 per cent) had good results (Table II).

The combination of 1/200 grain of scopolamine with 5 mg. of the drug apparently improved the effect.

Amnesia is not a property of drugs of this type; so we did not make special tests in an effort to determine this effect. Nevertheless, patients occasionally noted that they could not remember when they went to the delivery room, or the time of day, etc. Scopolamine does produce amnesia; so the mothers who received it were considered separately. When scopolamine was given, approximately half had fair amnesia, but without it there was no significant amnesia.

TABLE II. ANALGESIA AND REST IN RELATION TO DOSAGE

ANALGESIA	5 MG.	5 MG. PLUS SCOP. 1/200	7½ MG.	10 MG.	TOTAL
None	1	0	0	0	1
Poor	2	0	1	0	3
Fair	12	2	2	2	18
Good	7	6	1	0	14
Excellent	1	5	3	1	10
Not evaluated	2	1	0	1	4
	25	14	7	4	50
REST					
None	0	0	0	0	0
Poor	3	0	1	0	4
Fair	8	3	0	1	12
Good	7	6	2	2	17
Excellent	5	4	4	0	13
Not evaluated	2	1	0	1	4
	25	14	7	4	50

Effect on Labor

There is probably no more difficult observation to make than to determine the effect of any given drug on the duration of labor. So many variables are present that significance of any one is easily lost. To measure the effect of a drug in terms of duration of labor means a consideration of the effectiveness of uterine contractions, the state of the cervix and other soft tissues, the configuration of the bony pelvis and the size of the baby. Even if all of these could be measured, we still have no satisfactory method of determining the onset of labor.

Most labors gather momentum as they progress, but the amount of this increase and the time of its appearance cannot be predicted. There are, of course, many exceptions, such as secondary uterine inertia. In this study, we have attempted to evaluate the effect of No. 10720 on uterine contractions in the negative sense. That is, to ask: Was there a diminution in the frequency, intensity, and duration of contractions following the use of the drug?

With the foregoing qualifications in mind, our observations indicate that six mothers had a mild temporary diminution in the frequency of contractions. Three showed some temporary reduction of intensity of contractions. None

showed significant change in the duration of contractions. Of 39 women who received the drug during active labor, after cervical dilatation was under way, 34 were delivered in less than four hours and about half were delivered in less than two and one-half hours.

Delivery

Many methods of obstetric analgesia interfere with the normal mechanism of delivery, so that operative intervention frequently becomes necessary. No such tendency was evident in this study. Of 30 primiparous patients, 21 delivered spontaneously. There were 9 forceps deliveries; 5 were done electively because of complications of pregnancy; 2, and possibly a third, were done because of lack of progress in the second stage of labor, in spite of good contractions and excellent cooperation, and only one because of poor cooperation associated with effects of analgesia. Of the 20 multiparous patients, 2 low forceps deliveries were done. In both, the indication happened to be the same, previous cesarean section.

Blood Loss

Most of the women lost less than 300 c.c. of blood (estimated). Two had postpartum hemorrhage, but in neither case was the drug at fault.

Anesthesia

Frequently analgesics are blamed for effects produced by anesthesia at delivery. The converse is equally true. For this reason, no general anesthesia was produced. About two-thirds of these patients received nitrous oxide-oxygen analgesia combined with local anesthesia, and the remainder had local anesthesia or none at all.

Neonatal Asphyxia and Mortality

There is no standard classification for neonatal asphyxia. Something more than the textbook descriptions of asphyxia livida and asphyxia pallida is necessary. For a period of years we have used the following classification (Table III) which, although strict, is not too difficult to apply clinically. It is especially important that strict standards be used in the evaluation of analgesic agents.

TABLE III. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE ASPHYXIA
Respiratory	Onset respiration	Spontaneous, immediate	Spontaneous oligopnea 1 to 5 min.	Delayed apnea 5 to 15 min.	Delayed apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous, lusty	Delayed, vigorous, lusty	Delayed, weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous, active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

Fifty mothers were delivered of fifty-one babies. There were no stillbirths and three neonatal deaths. Two of the deaths were due to congenital disease incompatible with life, and the third infant died of meningitis. It is obvious that the drug was not a significant factor in these deaths.

The incidence of neonatal asphyxia was low. Eighty-two per cent of the babies were normal; 12 per cent had mild asphyxia; 6 per cent had moderate asphyxia, and there was no severe asphyxia.

Two easily measured objective signs were used in this classification of asphyxia: the onset of respirations, and the appearance of the characteristic lusty cry. Any infant who breathed spontaneously, in less than fifteen seconds "by the clock," was classified as having immediate respiration. This is about the usual length of time required to complete the delivery and to upend the baby for drainage of mucus and amniotic fluid. Forty-one had immediate respiration (Table IV). Two were delayed five minutes and four were delayed between two and three minutes.

TABLE IV. ONSET OF RESPIRATIONS AND CRYING

	RESPIRATIONS	ACTIVE CRY
Immediate	41	33
Within $\frac{1}{2}$ min.	1	-
Within 1 min.	1	3
Within 2 min.	3	3
Within 3 min.	1	2
Within 4 min.	0	0
Within 5 min.	2	3
Within 10 min.	0	2
Within 15 min.	0	2
No data	2	3
Total babies	51	51

The significance of the *active cry* for classification of asphyxia has not often been used and might be questioned by some as invalid. It is certain that perfectly normal babies without asphyxia and with normal respirations and color may fail to cry immediately or occasionally for several minutes. On the other hand, we have observed for many years that a delayed cry frequently indicates depression below the level of asphyxia. Before the baby can actually cry it must breathe; so we have classified as immediate any cry within thirty seconds after delivery. Two-thirds of all babies had an immediate cry, and the remainder were distributed rather evenly through the first fifteen minutes of life. One failed to cry—an infant with congenital absence of the diaphragm.

Many factors other than analgesia can produce neonatal asphyxia. Consequently each asphyxiated infant was carefully evaluated for cause of asphyxia.

Of the nine babies under consideration, two had congenital lesions responsible for asphyxia. Three were asphyxiated by difficult delivery. The drug was at fault in four cases, about 8 per cent. It produced three mildly asphyxiated babies and moderate asphyxia in one.

The next step was to determine in what way the drug was to blame. Was it a question of timing in relation to delivery? Was it dosage? Was it faulty evaluation of the patient as an asphyxial risk?

It is a well-established fact that small infants tolerate analgesics poorly. When these infants are sorted according to weight (Table V), it is evident that three of the four babies with asphyxia due to the drug were from a group of nine weighing less than 2750 Gm.

There was good evidence that dosage was also a factor in asphyxia. Forty mothers receiving no more than 5 mg. of No. 10720 as a terminal dose produced one mildly asphyxiated baby, while three were produced by eleven mothers who had received 7.5 or 10 mg. of No. 10720.

TABLE V. ASPHYXIA AND WEIGHT OF INFANT

WEIGHT IN GRAMS	TOTAL	ASPHYXIA
2250 to 2500	4	1 (d)
2500 to 2750	5	2 (2d)
2750 to 3000	6	1
3000 to 3250	11	4 (1d)
3250 to 3500	10	1
3500 to 4000	14	0
No data	1	0
	51	9 (4d)

(d) Asphyxia due to drug.

The relationship of "drug asphyxia" to the difference between time of administration and delivery is not clear. All of the babies so asphyxiated were delivered from one to three hours after the mother received the drug, but the majority of the babies were also delivered during this same time. If a time relationship exists, more experience will be necessary to establish it.

Special mention might be made of one group of twenty-one private patients who were included in this study. All but one received 5 mg. of the drug, usually combined with scopolamine. A general attempt was made to see that the drug was not administered to women with small babies and to those who would deliver within two hours. Every baby but one in this group breathed immediately, and one breathed in thirty seconds. Fifteen cried immediately, three in one minute, two in two minutes, and one in five minutes. The latter was mildly asphyxiated.

Results With Dolophine (No. 10820)

Dolophine was administered to 17 obstetric patients. The amount given ranged from 5 mg. to 15 mg. with a usual dose of 7.5 mg. Analgesia, such as it was, appeared in approximately one-half hour. The effect, when present, persisted for about two hours.

Untoward side reactions were not noted. Two women had nausea, and one was wildly excited. The excitation was present before, as well as after, use of the drug.

Twelve of the seventeen were observed closely for changes in pulse, respiration, blood pressure, and fetal heart rate. None were noted.

Analgesic effects were disappointing. There was no excellent nor good analgesia; one only had fair analgesia, while 7 had poor results, and 9 were failures. There was no amnesia. Rest was obtained in 11 patients; 6 had fair results, and 5 had poor rest.

There was no visible effect of the drug on the frequency, duration, or intensity of the contractions.

Two infants were mildly asphyxiated. The cause in one was trauma and, in the other, the drug (15 mg.) was to blame.

Discussion and Summary

These preliminary investigations have convinced us that compound No. 10720 is worthy of further trial as an obstetric analgesic. Dolophine (No. 10802), in our hands, has not been a useful agent.

From the results described, we have formulated a general plan for the use of this analgesic. It is well to wait until the patient is in active labor and in genuine discomfort before the drug is given. On the other hand, too much de-

lay permits labor to advance to a point where the drug cannot overcome the pain of the strong uterine contractions. Some of the poor results came when this error was made. The most satisfactory dose of No. 10720 is from 5 to 7.5 mg. This corresponds roughly to 100 mg. of demerol. Larger doses, 7.5 to 10 mg., may be given to mothers with normal-sized infants, if delivery is not imminent within three hours. The combination of 5 mg. of No. 10720 with 1/200 grain of scopolamine produced results comparable to those which followed the use of 7.5 mg. alone. The peak of analgesia is apparently reached in one and one-half hours, and most of the effect is lost within three hours. Thus the drug should not be given oftener than every three hours.

Generally speaking, it may be said that analgesia is satisfactory. Although we did not make direct comparisons with Demerol, which has been used for many years on this service, many of the staff think the new drug to be equal or superior.*

After administration of No. 10720, the patients usually become sleepy, and often they sleep soundly between contractions. With the onset of a contraction, they usually rouse and are aware of some discomfort. Excitement was not noted, and nearly every patient was able to cooperate fully, a fact of particular significance during the second stage of labor.

There was no evidence of interference with the effectiveness of the uterine contractions. About three-fourths of the women observed completed their labor in less than four hours after medication. This fact, combined with the fact that we attempted to give the drug before labor was far advanced, suggests that labor was not prolonged. The obstetric literature is replete with reports that this or that analgesic shortened labor. Before such statements can be considered valid, careful controls must be had from the same type of obstetric material in the same clinic. This we did not do.

Did the infants have to pay a price for the pain relief of their mothers? They probably did; but there was little evidence to indicate that they paid too much. There were three neonatal deaths, none of which could be attributed to the drug in any way.

There were nine asphyxiated infants (18 per cent). There were no controls with untreated mothers; however, we have previously expressed the incidence of asphyxia neonatorum in such patients,^{3, 4} at about 10 per cent, with a distribution 5 per cent mild, 4 per cent moderate, and 1 per cent severe asphyxia. In the present report there was 18 per cent asphyxia, with a distribution of 12 per cent mild, 6 per cent moderate, and no severe asphyxia. This suggests that No. 10720 causes some increase in mild asphyxia, which is of no great clinical significance. The fact that moderate and severe asphyxia are apparently not increased is of great clinical significance.

It was possible to assign four of the nine cases of asphyxia to the drug. Three of these were mild and one was moderate. The appearance of asphyxia in babies weighing less than 2750 grams again confirms the fact that small in-

*One patient in this group received No. 10720 as well as Demerol during labor. One hundred mg. of Demerol given during early active labor produced fair (2 plus) pain relief. Later in labor, 5 mg. of No. 10720 produced good (3 plus) pain relief.

infants tolerate analgesics poorly. Furthermore, 2 of these 3 mothers received 7.5 and 10 mg. of the drug, respectively. In retrospect, it is evident that the larger doses of No. 10720 should not have been given to mothers with small infants.

Judgment follows experience, and skill is the result of technique and practice. Both are necessary for the proper use of all methods of obstetric analgesia. Therefore we believe that the clinician who is not prepared to undertake a controlled investigative procedure should not forsake familiar standard practices until the value of a new drug is proved.

Conclusions

1. A new phenyl-piperidine compound similar to Demerol, as yet unnamed, but called compound No. 10720, has been tried as an obstetric analgesic in fifty labors.

2. The drug had few side reactions, and toxic manifestations were not seen.

3. Analgesia was fair to good in about two-thirds of the patients treated with 5 mg. of No. 10720. The addition of 1/200 grain of scopolamine seemed to enhance the analgesia. Amnesia was rarely present unless scopolamine had been given.

4. Asphyxia neonatorum was not a problem. Although there was some increase in mild asphyxia, there was no severe asphyxia, and only the usual amount (about 5 per cent) of moderate asphyxia.

5. Dolophine (No. 10820) was used in seventeen patients. As a whole, the results were disappointing.

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1542 TULANE AVENUE

A METHOD OF OBSTETRIC ANALGESIA AND ANESTHESIA*†

LEES M. SCHADEL, JR., M.D., PHILADELPHIA, PA.

(From the Hahnemann Medical College and Hospital, Departments of Obstetrics and of Anesthesiology)

ALTHOUGH no one ideal method of obstetric analgesia and anesthesia has been presented, it is thought that the combination to be described (Demerol and scopolamine) fulfills many requirements. The object of this study was the attainment of a simple, adequate method of obstetric analgesia which is safe enough to have wide application and adequate enough to provide analgesia and anesthesia for normal labor and outlet or low forceps delivery.

For the procedure selected, two drugs were employed which have a general analgesic and amnesic effect on the patient in the earlier stages of labor. Demerol was used for analgesia and scopolamine for amnesia. Since these alone are usually inadequate for the perineal stage and repair, local anesthesia in the form of a pudendal nerve block was selected. Demerol has been used in combination with scopolamine for the first and second stages of labor.^{1, 2} For the delivery and repair, a 1 per cent Intracaine solution was used for nerve block. General anesthesia has a depressing effect on the infant, and it is undesirable to administer a general anesthetic agent to the unprepared patient. Demerol, therefore, was chosen because it lacked respiratory depression in the therapeutic dosage when used with a pudendal block. Intracaine was chosen for pudendal block because it displays a more rapid action than procaine hydrochloride, yet it produces anesthesia of greater duration.³ Although the principle of pudendal block is not new,⁴ a simplified method is presented to permit its universal acceptance. Today, one-half of American women are delivered in the home, and nursing staffs of most hospitals are still feeling the effect of war shortages. This combination requires a minimum of professional and nursing care, yet allows the patient safe conduct through her first stages of labor with analgesia and amnesia, which is obtained by using Demerol and scopolamine. Minor obstetric procedures such as spontaneous delivery with episiotomy or low forceps may easily and safely be carried out by the use of pudendal block with Intracaine.

Technique

The foundation for a safe, painless delivery is an adequate psychological approach to childbirth as a physiologic phenomenon. If the developed fears of

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tion, obstruction, and poor drainage, enlarges sufficiently to become a urethral diverticulum.

Years ago Routh²⁷ noted that the urethral glands may become retention cysts by obstruction of their orifices through urethritis or periurethritis. As a result of suppuration or rupture, the cyst then opens again into the urethra and the inflammation continues. Urine finds access to the diverticular cavity at each urination and, owing to the small caliber of the opening, the distention of the cavity increases. It is undoubtedly true, as is often asserted, that the trauma resulting from pressure of the fetal head on the dorsal urethral wall may be sufficient to rupture the urethral musculature with the production of a urethral diverticulum at the time of labor. It seems more likely, however, that this trauma would produce a widespread tearing of the urethral walls and supports with the formation of a urethrocele rather than a minute hernial aperture through which a finger-like pouch of mucosa would protrude.

Cysts of the anterior vaginal wall and suburethral tissues are moderately frequent. While of interest, they rarely become large enough to concern the patient. Cullen²⁸ felt that vaginal cysts rarely, if ever, originated from urethral glands. He noted that a connecting link with the urethra is usually lacking in such cysts, and that origin from Gartner's ducts seemed more likely. In view of the present demonstration of the anatomy of the paraurethral glands, and the knowledge that they may extend into the deeper suburethral tissues, it seems quite possible that retention cysts of such structures might equally well cause cystlike tumors of the anterior vaginal wall. Cystic dilatation of the ducts and glands is common; frequently they are connected to a duct by a narrow epithelial channel which would be impossible to demonstrate at the time of surgical removal. The usual location for Gartner's ducts is in the lateral or anterio-lateral vaginal wall, and the presence of a duct remnant in the midline beneath the urethra would presume its deviation from a normal anatomic location.

Primary carcinoma of the female urethra is infrequent. Most of the reported cases are an epidermoid type of growth; adenocarcinoma is rare.²⁹ Most of the few adenocarcinomas are described as hard, rounded, nodular masses surrounding the urethra and without ulceration of the urethral mucosa. Whitehouse³⁰ states dogmatically that such adenocarcinomas originate in the paraurethral glands and are homologous to prostatic carcinomas of the male. Menville³¹ points out that the majority of early carcinomas of the urethra arise near the meatus and that a paraurethral duct emptying near the external urethral orifice where it is susceptible to infection and trauma may be a frequent site for a primary growth. Since the paraurethral structures contain intraepithelial mucous secreting glands and true branched tubular glands, it is understandable that adenocarcinomas may occasionally develop from them.

The channels of the paraurethral ducts have been shown to reach the outermost limits of the urethral core. Trauma to or severance of such a channel may explain some of the heretofore inexplicable urethral fistulas developing after an apparently perfectly performed urethrocele repair. In a like manner, an urethro-vaginal fistula may follow a paraurethral duct abscess which communicated with both the urethra and the vagina.

the tip and redirected to the symphysis. After aspiration, the ilio-inguinal nerve is blocked with 10 c.c. of Intracaine solution as the nerve passes over the symphysis. Again the syringe is disconnected and refilled with solution, replaced on the needle and directed toward, *but not into*, the sphincter ani muscle. Here 10 c.c. of solution are deposited in the levator fascia following aspiration, so that the inferior hemorrhoidal and branches of the fourth sacral nerves are blocked. This procedure is repeated on the other (right) side. After about five minutes, perineal relaxation is obtained and anesthesia is thus established. Skin test for satisfactory anesthesia is performed and its extent noted. A gauze sponge is clamped to the perineum so that the rectum is covered to prevent any contamination. This step further confirms satisfactory perineal anesthesia. Episiotomy may then be performed while rational conversation is exchanged with the patient. Labor may progress normally, or low forceps may be indicated with the completion of the second stage, and the third stage can be completed. Since the pudendal block does not eliminate sensory impulses from the cervix, undue traction must be avoided during its inspection. Should this procedure prove painful, or extensive cervical repair be necessary, 100 mg. of Demerol, given intravenously, will allow extensive surgical repair of the cervix, vagina, perineum, or rectum.

The series consisted of 100 study patients and 100 control patients divided into 60 primiparas, 40 controls, and 40 multiparas and 60 controls. Only patients who had normal spontaneous delivery were selected for controls after delivery and not at random on admission. The cases for study were selected at random on admission; the criteria were a normal pelvis and a prospective normal delivery.

Complications in the study group existing at the onset of labor were: mild pre-eclamptic, 10, cardiac, 1, multiple pregnancy, 1, premature labor, 2, and tracheobronchitis, 1. In the control group there was 1 premature labor. Complications and surgical procedures during labor in the study group were: twins, 1, persistent occiput posterior, 1, elective outlet forceps, 17, surgical forceps, 2, spontaneous breech, 1, and secondary uterine inertia, 1. The controls showed no complications of labor since they were selected after delivery. There were no serious complications of labor and there was no maternal mortality. The maternal morbidity in the study group included postpartum hemorrhage, 2 cases, mild endometritis and parametritis, 7 cases, infected episiotomy, 1 case, retained secundines, 2 cases, and ischiorectal abscess, 2 cases. The control group included 10 patients with parametritis and 2 with ischiorectal abscess.

Fetal Mortality

Two fetal deaths occurred in the test group, a fetal mortality of 2 per cent. Both of these were neonatal deaths resulting from intracranial trauma. In Case 1, precipitate delivery, neonatal death occurred thirty-six hours after delivery. The infant had received continuous oxygen therapy after thorough aspiration. Postmortem examination disclosed bilateral tentorial tears and atelectasis in four lobes of the lungs. Consequently, the method of anesthesia was not responsible for the death.

Case 2 was also a neonatal death, which occurred eleven hours after delivery of a premature infant whose birth weight was 2 pounds 15 ounces. This infant was cyanotic and received oxygen and incubator care. Postmortem examination revealed a subdural hemorrhage; consequently, the method of analgesia was not responsible for this death.

the expectant mother can be minimized, one may enjoy complete cooperation throughout labor. When the uterine contractions elicit severe pains during the first stage of labor, a rectal examination is performed to determine the condition of the cervix and the progress of labor. If the cervix is dilated 4 cm. or more and strong painful contractions are present, Demerol and scopolamine are given. Demerol, 1 mg. per pound of body weight, and scopolamine hydrobromide, $\frac{1}{150}$ grain, are now administered intramuscularly. Although mixing these solutions is not recommended, Demerol can be given intravenously, if desired, without harmful effects. Most patients will obtain moderate to complete relief of pain for from two to four hours without any significant retardation in labor. After this period, additional analgesia may be required and safely repeated, provided the progress of labor is satisfactory. Occasionally, sensitivity to scopolamine may make it desirable to reduce the amount of scopolamine to $\frac{1}{200}$ grain to prevent irrational behavior.

When the progress of labor has advanced and rectal examination reveals that the cervix is completely dilated in the multiparous patient, or the perineal stage is reached in the primiparous patient, preparation for delivery and pudendal block is completed by placing the patient on the delivery table in the lithotomy position. Since the effectiveness of this technique lies in adequately blocking the pudendal, ilio-inguinal and inferior hemorrhoidal nerves, knowledge of their anatomic distribution is essential. The pudic nerve (n. pudendus) is the principal nerve supply of the perineum. Its origin in the pelvis is usually from three roots arising from the second, third, and fourth sacral nerves. The pudendal nerve passes to the buttock through the great sacrosciatic foramen below the great sciatic nerve and lies on the lesser sacrosciatic ligament or the spine of the ischium. It is mesial to the internal pudic artery and enters the perineum with the pudic artery through the small sacrosciatic foramen. In the perineum, it is deeply placed in the outer wall of the ischiorectal fossa, enclosed in a special sheath derived from the parietal pelvic fascia called Aleock's canal, which contains the pudic nerve, artery, and vein. It is at this point, mesially to the ischial tuberosity, where the pudendal nerve is blocked, and not at the usual site at the spine of the ischium. Occasionally the inferior hemorrhoidal nerve has an independent origin from the plexus and merely accompanies the pudic nerve in the first part of its course. The cutaneous branch of the ilio-inguinal nerve which innervates the skin over the symphysis, the mons veneris, and labium majus forms continuous branches with the pudendal or pudic nerves. For this reason, the ilio-inguinal and inferior hemorrhoidal nerves are given special attention.

Surgical preparation of the perineum includes cleansing the previously shaved area with soap solution. Zephiran solution, 1:1,000, is used for the skin antiseptic, after which sterile drapes are applied. The sterile pudendal-block kit is then opened and the solution prepared by placing 1 Gm. of Intracaine crystals in a flask containing 100 c.c. of distilled water. To this, five drops of epinephrine solution, 1:1,000, is added. The rectum is covered and a skin wheal is raised on each side of the perineal body with a hypodermic needle, using Intracaine. This blocks the cutaneous nerves to the perineum from the inferior pudic nerve. The left index finger is inserted into the vagina and pressure is exerted to the left and laterally to the tuberosity of the ischium, thereby, compressing Aleock's canal. Through the skin wheal, the 3 inch, 20 gauge, needle is directed to Aleock's canal. It is guided into this position by the left index finger and the tuberosity of the ischium. When this site is located and after the preliminary aspiration, 10 c.c. of 1 per cent Intracaine solution is injected along the pudendal nerve. Without removing the needle, the 10 c.c. syringe is disconnected and refilled, reconnected to the needle which is withdrawn almost to

The Result of Analgesia and Anesthesia

Satisfactory anesthesia was demonstrated by skin test and by a statement of the patient twenty-four hours later to the same impartial observer (Table I).

TABLE I. EFFECTIVE ANALGESIA

	SATISFACTORY	UNSATISFACTORY
Study group	90	10
Control group	50*	50

*Some had nitrous oxide and oxygen at birth of head.

Comment

The use of Demerol for analgesia is a contribution to obstetric practice. In the dosage recommended, it may be considered safe when given within one hour of delivery if local block is used for the second stage of labor. The following contraindications exist:

1. Local infection of the perineum, bacterial or fungus (at the site of injection). Included are cryptitis and infected thrombotic hemorrhoids.
2. Hysteria, epilepsy, or emotional instability.
3. Obstetric complications (about 4 per cent of hospital patients).
 - a. Placenta previa.
 - b. Placenta abruptio.
 - c. Cephalopelvic disproportion, unless the Demerol and scopolamine are used as analgesics during a test labor.
 - d. Birth of monstrosities.
 - e. Patients with unengaged head or false labor.
 - f. History of previous sensitivity to either drug—exceedingly rare.

No attempt was made to study the effect of Demerol on pre-eclamptic patients. Ten such patients with mild to moderate symptoms showed no unusual reactions.

The intravenous method of administering Demerol is not contraindicated in the recommended dosage. Regardless of the speed of intravenous administration, no deleterious reactions were observed in over 200 injections. There was no infant or maternal mortality, nor was there infant respiratory depression. Slight depression of the infant has been known to occur when barbiturates or nitrous oxide and oxygen were used. Intracaine is ideal, since it is a quick-acting local anesthetic of long duration. With proper technique, the area of anesthesia extends two-thirds the length of the vaginal canal, and visible relaxation through the perineum may be noted. No fear of respiratory depression need exist, since the patient is able to converse with her obstetrician during the repair. Demerol may be used in obstetrics without fear of addiction, and it requires a minimum of obstetric experience to determine accurately the optimal time for Demerol analgesia and the performance of a pudendal block. The technique has been simplified so that the pudendal nerve is blocked at its exit from Alcock's Canal.

The duration of labor in the 60 primiparas of the test group ranged from three and one-half hours to twenty-four hours; in the control group it varied from six and one-half hours to twenty-four hours (Fig. 1). In the test group of 40 multiparas the duration of labor ranged from one and three-fourths hours to twenty-eight and one-half hours, while in the control group it ranged from one and three-fourth to fifteen hours (Fig. 2). The average dosage used was 1 mg. per pound of body weight. This was repeated in two hours when necessary, since the effective duration was from two to four hours. Consequently, the total average dose was 200 milligrams.

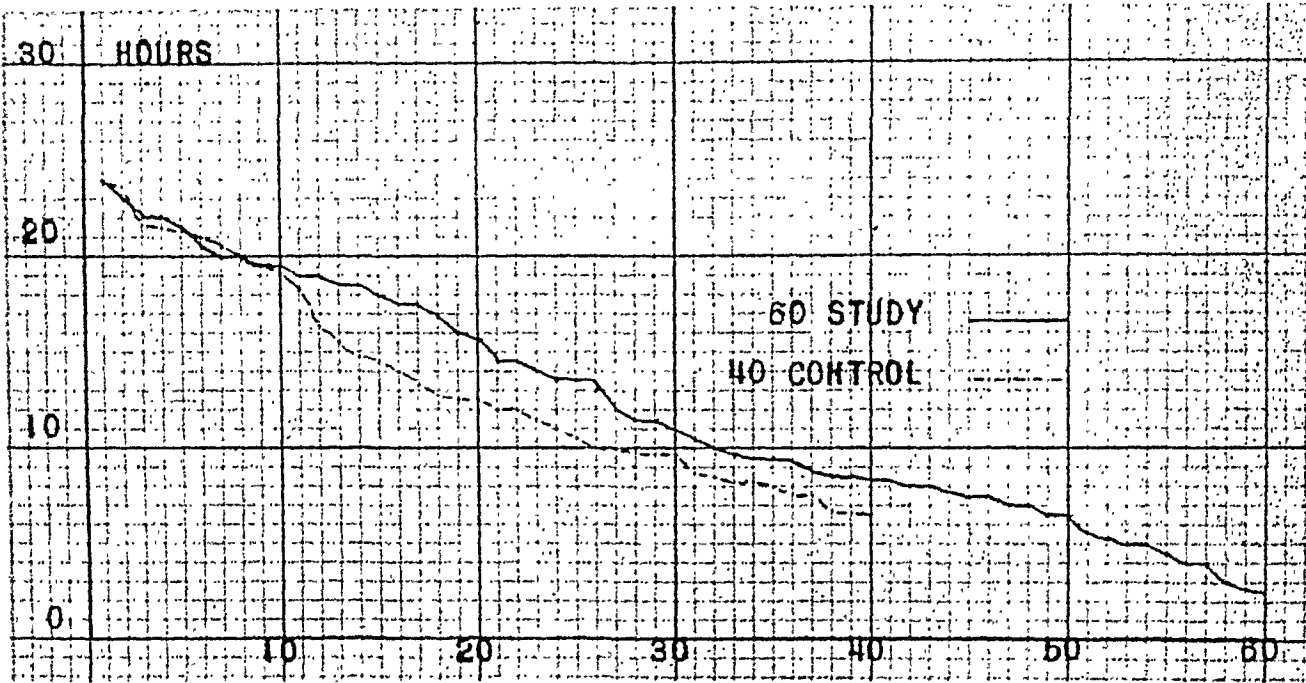


Fig. 1.—Duration of labor—primiparas.

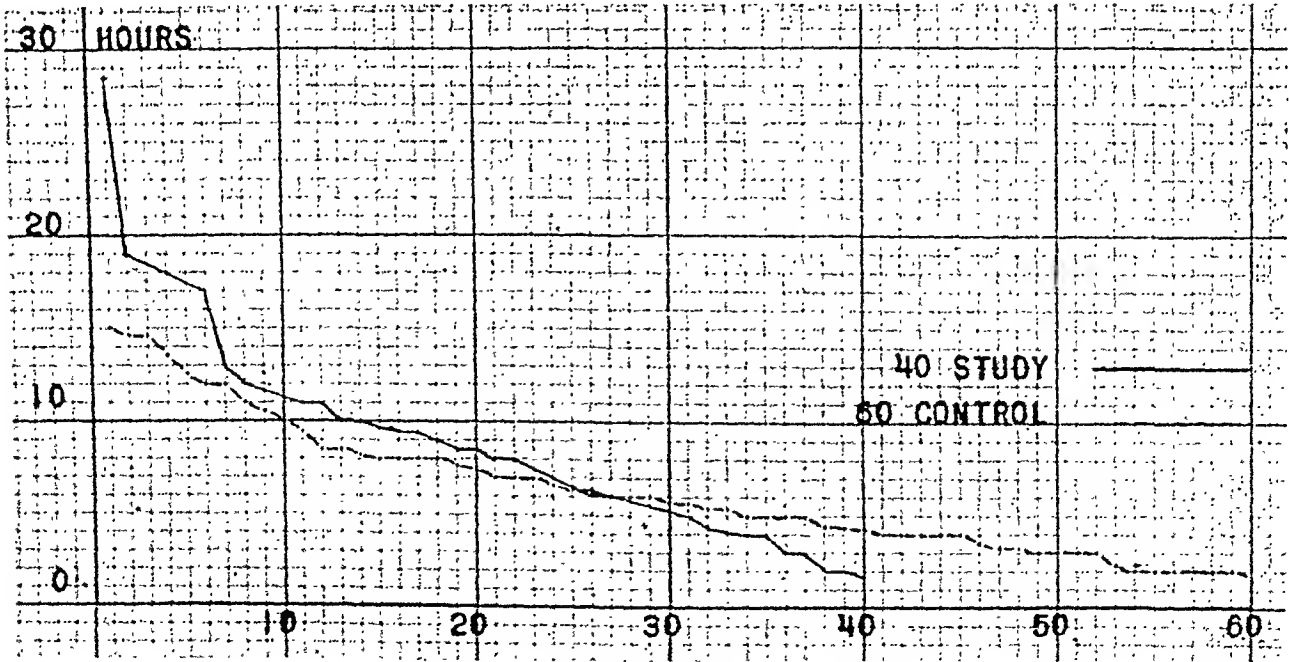


Fig. 2.—Duration of labor—multiparas.

weighing 170 pounds, was given 200 mg. of Demerol. This patient was in good physical condition. Physical examination was essentially negative with pregnancy at term. At the end of approximately fifty-five minutes of active labor, she was given 200 mg. of Demerol intravenously, the time during which it was administered being approximately one and one-half minutes. During the period of injection, conversation was carried on between the operator and the patient. Immediately following the administration of the Demerol, scopolamine hydrobromide, with $\frac{1}{200}$ grain in the syringe was started intravenously. To give this injection was to take two minutes. By the time one-half of the scopolamine was injected, the patient had ceased talking, showed mild cyanosis, and absence of any respiratory efforts. Oxygen was administered and at first it was necessary to inflate the lungs a few times. Then she began to breathe spontaneously at the rate of four per minute. Her respiratory rate gradually increased so that by the end of two hours the rate was 8 per minute. Twenty minutes after the Demerol was given, the patient delivered spontaneously without any additional anesthesia. The baby cried vigorously at birth.

There have been occasions, however, when we have been suspicious of some degree of respiratory depression from Demerol in the newborn. On the matter of the nerve supply to the perineum, there is one additional nerve that should be described, the inferior pudendal nerve. This arises from the posterior femoral cutaneous or small sciatic nerve near the lower border of the gluteus maximus muscle and passes downward and in front of the tuberosity of the ischium and continues anteriorly in the subcutaneous tissue of the perineum to supply the scrotum in the male and the labium majus in the female. Failure to block this nerve will result in inadequate anesthesia of the perineum. Also, in the diagram showing the placement of the needles, I do not believe the fact was mentioned that the needle was directed subcutaneously toward the symphysis. It does not go beneath the deep fascia because the terminal filaments of the ilio-inguinal nerve are in the subcutaneous tissue. The use of Adrenalin was mentioned, and I mention it now to endorse it heartily. We make it a practice with few exceptions to add Adrenalin to local anesthetic agents. The matter of aspiration cannot be overemphasized. An additional procedure to make certain that a needle is not within a blood vessel is to aspirate while rotating the needle through a circle, aspirating about one time in every quadrant as the needle is rotated. It is possible for a needle to be within a blood vessel and on aspiration to have no blood appear in the syringe for the simple reason that the intima of the blood vessel is drawn against the needle, thereby blocking it. It is unlikely that a needle will be in a blood vessel after having aspirated repeatedly while rotating the needle through a complete circle. I consider the use of pudendal block a valuable procedure and particularly useful in those circumstances in which facilities are limited.

DR. ROBERT M. HUNTER.—I think I should say something concerning the six cases of ischiorectal abscess reported by Dr. Schadel.

I happened to be on service at the time, and feel that it was lack of training on the part of the interne staff that produced the abscesses. He did not, but should have defended himself. He should have stated that in the cases he personally supervised no ischiorectal abscess developed. The interne failed to realize the displacement of the rectum during the last stages of labor, and thus the needle inadvertently perforated the roof of the rectum.

This error has been corrected and since that time we are glad to report there has been no further such unpleasant sequela.

DR. SCHADEL (Closing).—It was interesting to me that Dr. Paxson noted that 50 per cent of those patients receiving no anesthesia had essentially no pain at delivery. That point interests all of us. We should, therefore, recognize that fact and whatever we give as an analgesic agent should not jeopardize the patient's life. The instance of shock in giving 200 mg. of Demerol intravenously was something I had not experienced in using a dosage of 1 mg. per pound of body weight. I was, unfortunately, not able to see any cases where there was that reaction. In no instance was there any demonstrable cyanosis in infants who had received Demerol and were delivered with pudendal block. However, there were instances of mild cyanosis in infants who were delivered under barbituric acid derivatives with nitrous oxide and oxygen. The nerve which Dr. Grove so adequately described was inadvertently blocked when the skin wheal was raised on the perineum.

This series has shown that three conditions must be present: (1) reasonable emotional stability in a patient who has not become irrational from too much scopolamine; (2) an adequate knowledge of the anatomy of the perineum by the physician, and (3) vigilance to aseptic technique and consciousness that this is a local anesthesia. When these qualifications are fulfilled, a wide variety of common obstetric procedures, including episiotomy, low forceps, and perineorrhaphy, may be performed.

Summary

A safe, simple, efficient method of obstetric analgesia and anesthesia has been described, using some new synthetic drugs. The large factor of safety of Demerol in combination with scopolamine and Intracaine offers a procedure without any of the hazards of the more common types of anesthesia, particularly when the services of a professional anesthetist are not available. The simplicity of this technique is apparent when an elementary knowledge of the anatomy of the perineum is acquired. It is effective when the nerves are blocked and allows most minor procedures, including outlet forceps delivery and repair.

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Discussion

DR. NEWLIN F. PAXSON.—This was a project we have been working on at Hahnemann with the idea of trying to find a safe procedure that would have application not only in the large hospitals, but in the small hospitals, and in the homes, where elaborate preparations are not possible. It seems to be a fairly practical method.

The reason for the selection of the particular drugs used is that they fulfill most nearly the requirements of simplicity and efficiency. The barbiturates cause too much restlessness; also, when they are supplemented by nitrous oxide and oxygen administered by an unskilled anesthetist, deaths have followed.

The occurrence of two ischiorectal abscesses is due primarily to the blocking of the sacral nerves. This particular hazard can be overcome by injection around the anus subcutaneously. The needle enters the original wheal and is pointed toward the anus; 5 c.c. of Intracaine is then injected above and lateral to the anus.

There is one interesting thing I observed, the report of satisfactory analgesia on the part of controls who received little or no analgesia at all, except inhalation for the perineal stage. The only way we have of estimating the results of a method of obstetric analgesia is to ask the patient whether the method is satisfactory. Apparently a great many women are satisfied with any method that does not leave them uncomfortable for a long period. This may explain why so many methods are reported as satisfactory.

DR. DWIGHT GROVE.—My discussion tonight will be more from the standpoint of anesthesiology than from obstetrics. It is generally said that Demerol produces more analgesia with less respiratory depression than any of the more commonly used analgesic drugs. My experience would tend to bear out this statement. However, that Demerol can produce severe respiratory depression is illustrated by a case from our records. A 39-year-old multipara,

that in which 10 mg. of hyaluronidase was packed into the cervix, designedly before coitus. Details were given of six patients in whom pregnancy followed the utilization of the second method. Criteria governing their choice of patients were given. Proof of ovulation was furnished in their cases by endometrial biopsy. Estimation of ovulation time for use of hyaluronidase was carried out by the vaginal smear method of Papanicolaou and Shorr.⁷

It was not made clear in their paper whether these successful cases were six of a larger series by the packing technique or the only ones in which hyaluronidase was used in an effort to overcome sterility. Nor did they give data about relative merits of the two techniques when clinically applied, referring at one time to the packing technique and at other times to artificial insemination.

Present Study

We report herewith our lack of success in the use of bull testis hyaluronidase by the two methods mentioned by Kurzrok. The series consisted of 25 couples in whom a total of 67 trials with the enzyme were carried out.

The following criteria were utilized in a selected number of cases in which we used hyaluronidase:

1. Any or all faults of the female partner had been corrected as far as possible. Endometrial biopsies were resorted to in proof of ovulation.

2. Major faults in the male partner were corrected when possible. Those husbands with subnormal sperm specimens received appropriate treatment. Specimens of seminal fluid might show reduced numbers of spermatozoa, excessive percentages of abnormal forms, impaired motility, or a combination of any or all of the above. Many of the male specimens fell within normal values.

3. Better to evaluate the efficacy of hyaluronidase, therefore, its use was reserved for those couples in whom the ordinary current methods had failed to result in conception. These are the patients for whom, ordinarily, artificial insemination has been reserved, using husband's specimens, chiefly in the belief that some minor mechanical fault might be a factor.

Without making assays of hyaluronidase content of seminal fluid in these cases, we naturally assumed from Kurzrok's work that the specimens might be deficient or lacking in hyaluronidase, and we were encouraged to believe from what he and co-workers had presented, that the addition of hyaluronidase might be a valuable feature of artificial insemination.

Methods

In the early part of the study, artificial inseminations were carried out in a series of patients, using freshly obtained seminal fluid of the husband, collected usually after seven to eight days abstinence. Twenty mg. of bull testis hyaluronidase* was mixed with 1.0 c.c. of the seminal fluid and 0.5 c.c. of the resultant mixture introduced into the cervix. Insemination was performed usually on the first and third days closest to the ovulation period, as calculated by means of

*The bull testis hyaluronidase was provided by Dr. Erwin Schwenk of the Schering Corporation.

HYALURONIDASE IN TREATMENT OF HUMAN STERILITY*

RALPH E. TAFEL, M.D., PAUL TITUS, M.D., AND WILLIAM W. WIGHTMAN, M.D.
PITTSBURGH, PA.

(From the John C. Oliver Memorial Research Foundation and the Departments of Obstetrics-Gynecology, and of Urology, St. Margaret Memorial Hospital, Pittsburgh, Pa.)

IN A recent report, Kurzrok, Leonard, and Conrad¹ announced the use of bull testis hyaluronidase in the treatment of certain types of relative human sterility, reporting favorable results in six couples.

Hyaluronidase, an enzyme belonging to the group of so-called "spreading factors," is a component of normal spermatic fluid. It is said to be capable of bringing about the dispersion of the follicle cells surrounding recently ovulated ova of certain mammalian species by its property of breaking down intercellular cement substance, thus making possible the penetration of the ovum by the sperm.

Literature

The background for the therapeutic use of hyaluronidase in human sterility, as well as an introduction to its chemical relationships, has been outlined by Kurzrok et al.¹

Briefly, the steps leading to the application of the enzyme hyaluronidase to the problem of human sterility may be shown as follows:

1. The demonstration of McClean and Rowlands,² and also by Fekete and Duran-Reynals,³ later confirmed by Leonard and Kurzrok,⁴ that hyaluronidase possesses the property of dispersing the follicle cells of the corona radiata of mammalian ova. This removal of the cells surrounding an ovum is apparently a prerequisite to penetration of the ovum by a sperm.

2. The successful attempts by Rowlands⁵ to accomplish fertilization in rabbits with artificial insemination by the addition of hyaluronidase to sperm samples ordinarily numerically inadequate to produce fertilization.

3. The finding of Werthessen et al.,⁶ corroborated by Kurzrok's group, that, usually, there is a direct relationship between sperm numbers and hyaluronidase content of human semen.

4. The impression, shared by many workers in the field of human sterility, that, in couples wherein the husband's spermatic fluid is mildly deficient, the failure to conceive must be due to something more than merely diminished mathematical chances of a union between an ovum and a sperm.

In the study of Kurzrok and his colleagues referred to in the first paragraph, it is stated that hyaluronidase was used by them by two different techniques. One method involved the addition of 10 to 20 mg. of bull testis hyaluronidase to seminal fluid used for artificial insemination. The other method was

*First of three papers on hyaluronidase studies.

TABLE I. CLINICAL DETAILS OF HYALURONIDASE STUDY

CASE NO.	HISTORY	FEMALE FAULTS AND TREATMENT	REPRESENTATIVE SEMINAL SPECIMEN	INSEMINATIONS OR CERVICAL APPLICATIONS WITH HYALURONIDASE	RESULTS AND REMARKS
1. P. M.	Married 4 yr. Primary sterility. 3 yr. observation.	Severe menstrual cramps. Moderate tubal obstruction.* D. and C. and suspension, 1944. Insufflations, gonadophysin.	July 29, 1946. 90% motility. Total count, 1,020,000,000. 14% abnormal.	June 24, 1946, insemination June 26, 1946, insemination July 29, 1946, insemination July 31, 1946, insemination Sept. 30, 1946, insemination Oct. 1, 1946, insemination Dec. 29, 1946, insemination June 25, 1946, insemination June 27, 1946, insemination.	Negative
2. M. F.	Married 10 yr. Primary sterility. 6 yr. observation.	Endometriosis; cicatricial stenosis of cervical canal. Unilateral salpingo-oophorectomy. Dilatation of stenosis.	May 14, 1946. 90% motility. Total count, 35,000,000. 40% abnormal.	June 25, 1946, insemination June 27, 1946, insemination.	Negative
3. E. J. T.	Married 6 yr. Secondary sterility. (1 miscarriage at 2 mo., Feb., 1945). 1 yr. observation.	Retroflexion of uterus. Moderate tubal obstruction. Pessary, insufflations.	June 28, 1946. 70% motility. Total count, 180,000,000. 14% abnormal.	June 28, 1946, insemination. June 30, 1946, insemination. Feb. 21, 1947, packing.	Became pregnant when cervix was packed with hyaluronidase, Feb. 21, 1947.
4. E. W.	Married 11 yr. Secondary sterility. (Normal delivery Feb. 26, 1942). 2 yr. observation.	Low B.M.R. Moderate tubal obstruction. Thyroid medication and insufflations. (4 previous artificial inseminations without hyaluronidase.)	Oct. 11, 1946. 90% motility. Total count, 650,000,000. 20% abnormal.	Oct. 11, 1946, insemination.	Negative
5. M. F.	Married 8 yr. Primary sterility. 2 yr. observation.	Moderate tubal obstruction. Insufflations. (3 previous artificial inseminations without hyaluronidase.)	Oct. 18, 1946. 90% motility. Total count, 100,000,000. 20% abnormal.	July 12, 1946, insemination. Aug. 28, 1946, insemination. Aug. 30, 1946, insemination. Jan. 17, 1946, insemination. Jan. 20, 1946, insemination.	Negative
6. J. S.	Married 18½ yr. Primary sterility. 10 yr. observation.	Irregular periods and tubal obstruction, moderate. Heavy folds of vaginal tissue. Insufflations.	June 19, 1946. 49% motility. Total count, 492,000,000. 19% abnormal.	July 17, 1946, insemination Oct. 18, 1946, insemination	Became pregnant Nov., 1946, with one period intervening between last insemination and pregnancy

*The term "moderate tubal obstruction" as used in this chart means that passage of gas on tubal insufflation took place at higher than average pressure ranges.

rectal temperature readings.⁸ In several instances, insemination was possible only once within the ovulation period.

Because of a consistent lack of success, namely, no resulting pregnancies with this method, we then turned to the other method suggested by Kurzrok for the later part of the study. This technique is, as stated above, the packing of 10 mg. of hyaluronidase into the cervix on or about the day of the "ovulation temperature rise," instructing the couple to have intercourse within a few hours. A number of the couples who were treated with the packing technique were among the group previously receiving artificial insemination of seminal fluid with hyaluronidase.

Results

No pregnancies occurred in these 12 couples from artificial insemination, despite the fact that a total of 34 inseminations were practiced.

In only one instance did pregnancy follow a treatment with hyaluronidase, and that in Case 3 (E. J. T.), wherein cervical packing with hyaluronidase was practiced on the eleventh day of the cycle. This patient usually had twenty-six day cycles. She had received two artificial inseminations with hyaluronidase previously without result.

Lest too much merit be attributed to either of these two methods, it is interesting to note that one of our patients who was given artificial insemination with hyaluronidase had a normal menstrual period after the last insemination, and, following that period, became pregnant without any treatment. This couple with primary sterility had been married for eighteen years. We do not attribute this pregnancy in any way to the use of hyaluronidase, but reflected how easily we could have been misled in conclusions, if no menstrual period had intervened.

An interesting sidelight was the reaction experienced by patient No. 18 (W. J.) who, with each of the three cervical packings with hyaluronidase, experienced symptoms which are probably manifestations of an individual sensitivity to the enzyme preparation.

In order to place on record in detail the criteria for cases in this study, charts are submitted herewith. (Table I.)

Summary and Conclusions

1. A certain average amount of hyaluronidase in the seminal fluid is apparently essential for conception. Hyaluronidase is said to act by causing dispersion of the follicle cells surrounding the ovum, a necessary preliminary to the penetration of a sperm.

2. Theoretically, it would seem, in a sterile couple, that the addition of hyaluronidase to seminal fluid not grossly defective, but heretofore ineffective, should be a valuable adjunct in the use of such fluid for artificial insemination.

3. In spite of apparently favorable reports from other investigators, our findings with artificial insemination with hyaluronidase-treated seminal fluid, in a small series of cases, were entirely disappointing, no pregnancies resulting.

4. We are now investigating Kurzrok's second technique, namely direct application of hyaluronidase to the cervix at ovulation time, to be followed by normal coitus.

5. Of 18 couples in whom this latter "packing" technique has been tried, pregnancy has followed in only one instance.

Summary

The material studied consisted of serial sections and wax model reconstructions of adult human female urethras. As a result of this study, a concept of the anatomy and histology of the paraurethral ducts is presented. It would appear that these ducts are not constant in number or location; that they not only form extensive ramifications throughout the tissues about the distal urethra, but that they may also extend to within a short distance of the bladder; and that the often numerous ducts terminate in tubular glands which are lined for the most part by columnar epithelium. This epithelium has some, although limited, secretory activity.

The role which the paraurethral ducts may play in the etiology of lesions of the urethra and anterior vaginal wall is discussed.

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7. D. H.	Married 2 yr. Primary sterility. 18 mo. observation.	Moderate tubal obstruction; narrow cervix. Insufflations, dilatation of cervix (4 previous artificial inseminations without hyaluronidase.)	Oct., 1945. 50% motility. Total count, 16,000,000. 13% abnormal.	Oct. 28, 1946, insemination. Dec. 23, 1946, insemination. Jan. 15, 1947, insemination. Feb. 14, 1947, insemination. Mar. 31, 1947, packing. Apr. 25, 1947, packing. May 19, 1947, packing.	Negative
8. Y. F.	Married 3 yr. Secondary sterility. (One stillborn infant 2 yr. ago). 18 mo. observation.	Endoecervicitis. Low B.M.R. Moderate tubal obstruction. Cautery, thyroid medication, insufflations.	Mar. 25, 1946. 50% motility. Total count, 88,000,000. 25% abnormal.	Oct. 23, 1946, insemination. Nov. 27, 1946, insemination. Jan. 17, 1947, insemination.	Negative
9. F. H.	Married 9 yr. Primary sterility. 2½ yr. observation.	Retrodysplacement. Moderate tubal obstruction. Pessary, repeated insufflations.	"Specimen within normal limits" (report of outside urologist). May 8, 1946. 60% motility. Total count, 275,000,000. 18% abnormal.	Apr. 10, 1947, packing. May 7, 1947, packing. June 2, 1947, packing. July 24, 1946, insemination. July 26, 1946, insemination. May 2, 1947, packing.	Negative
10. F. C.	Married 6 yr. Primary sterility. 1 yr. observation.	Moderate tubal obstruction. Secondary anemia. Insufflations, and ferrous sulfate	Sept. 9, 1946, 90% motility. Total count, 67,000,000. 22% abnormal.	May 29, 1947, packing. May 29, 1947, packing. Dec. 16, 1946, insemination. Dec. 18, 1946, insemination.	Negative
11. G. P.	Married 9 yr. Primary sterility. 1 yr. observation.	Anemia, irregular periods. Ferrous sulfate.	Oct. 12, 1946. 85% motility. Total count, 225,000,000. 24% abnormal.	Jan. 8, 1947, insemination. Jan. 10, 1947, insemination. Feb. 5, 1947, packing. Mar. 5, 1947, packing. Apr. 14, 1947, packing.	Negative
12. K. N.	Married 3½ yr. Primary sterility. 1 yr. observation.	Small ovarian cyst. Cervicitis. Moderate tubal obstruction. Tubal insufflations, cauterization of cervix.	Apr. 29, 1946. 100% motility. Total count, 370,000,000. 18% abnormal.		Negative
13. R. N.	Married 1½ yr. Primary sterility. 1 yr. observation.	Cicatricial stenosis of cervical canal. Low B.M.R. Moderate tubal obstruction. Dilatation, thyroid medication, insufflations.	May 7, 1947. 70% motility. Total count, 40,000,000. 19% abnormal.	May 18, 1947, packing.	Negative
14. A. H.	Married 16 yr. Primary sterility. 6 mo. observation.	Retroflexion of uterus. Low B.M.R. Moderate tubal obstruction. Pessary, thyroid medication, ferrous sulfate, insufflations.	June 11, 1947. 90% motility. Total count, 75,000,000. 20% abnormal.	May 22, 1947, packing.	Negative
15. L. S.	Married 6½ yr. Primary sterility. 1 yr. observation.	Low B.M.R. Subserous fibroids. Thyroid medication, myomectomy.	Aug. 10, 1946. 95% motility. Total count, 320,000,000. 14% abnormal.	Apr. 14, 1947, packing. May 13, 1947, packing. June 6, 1947, packing.	Negative
16. R. E. H.	Married 3 yr. Primary sterility. 2½ yr. observation.	Low B.M.R. Moderate tubal obstruction. Thyroid medication, repeated insufflations.			

TABLE I.—CONT'D

CASE NO.	HISTORY	FEMALE FAULTS AND TREATMENT	REPRESENTATIVE SEMINAL SPECIMEN	INSEMINATIONS OR CERVICAL APPLICATIONS WITH HYALURONIDASE	RESULTS AND REMARKS
17. P. V.	Married 16 yr. Primary sterility. 2½ yr. observation.	Moderate tubal obstruction. X-ray Skiodan acacia shows patency. Repeated insufflations. Low B.M.R. Thyroid extract.	July 23, 1947. 75% motility. Total count, 154,000,000. 14% abnormal.	Apr. 21, 1947, packing. May 14, 1947, packing. June 16, 1947, packing.	Negative
18. W. J.	Married 17 yr. Primary sterility. 1 yr. observation.	Repeated insufflations. Low B.M.R. Thyroid extract.	Mar. 29, 1947. 95% motility. Total count, 385,000,000. 16% abnormal.	Apr. 4, 1947, packing. May 2, 1947, packing. May 28, 1947, packing.	General malaise, vulvovaginal itching, burning, abdominal aching and cramping, and coughing, and sneezing, and lachrymation after each treatment. Negative
19. W. T.	Married 6 yr. Secondary sterility. (One child, July, 1944.) 6 mo. observation.	Low B.M.R. Thyroid medication.	Jan. 24, 1947. 50% motility. Total count, 600,000,000. 17% abnormal.	May 22, 1947, packing.	Negative
20. J. C. M. K.	Married 15 yr. Secondary sterility. (One child, June, 1934.) 10 yr. observation.	Irregular periods. On Gonadophysin.	May 5, 1947. Total count, 285,000,000. 19% abnormal.	May 22, 1947, packing.	Negative
21. C. D.	Married 5 yr. Primary sterility. 2 yr. observation.	Moderate tubal obstruction. Repeated tubal insufflations.	Feb. 28, 1947. 95% motility. Total count, 1,050,000,000. 20% abnormal.	June 9, 1947, packing.	Negative
22. J. P. W.	Married 4½ yr. Primary sterility. 4 yr. observation.	Low B.M.R. Moderate tubal obstruction. Repeated tubal insufflations. None.	Mar. 18, 1947. 50% motility. Total count, 60,000,000. 33% abnormal.	June 10, 1947, packing. June 12, 1947, packing.	Negative
23. R. J. F.	Married 7 yr. Primary sterility. 18 mo. observation.	None.	Mar. 1, 1947. 95% motility. Total count, 20,000,000. 27% abnormal.	Apr. 10, 1947, packing. May 12, 1947, packing.	Negative
24. J. F. R.	Married 6½ yr. Primary sterility. 3 yr. observation.	Retrodisplacement. Moderate tubal obstruction. Low B.M.R. Pessary, repeated insufflations, thyroid medication.	Nov. 13, 1946. 15% motility. Total count, 20,000,000. 27% abnormal.	Feb. 10, 1947, insemination. Mar. 14, 1947, insemination. Apr. 4, 1947, packing. May 6, 1947, packing.	Negative
25. D. S.	Married 2 yr. Primary sterility. 6 mo. observation.	Moderate tubal obstruction. Repeated insufflations.	Apr. 4, 1947. 60% motility. Total count, 60,000,000. 43% abnormal.	June 4, 1947, packing.	Negative

6. The lone favorable result in twenty-five sterile couples treated with hyaluronidase would suggest that recent reports on the use of this enzyme in the treatment of human infertility are overoptimistic.

7. The study on which this preliminary report is based, is being continued in other phases.

George H. Fetterman, M.D., Director of Laboratories, St. Margaret Memorial Hospital, initiated and has directed the details of this, the first of a short series of studies on this subject.

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POLIOMYELITIS IN PREGNANCY

HOUGHTON GIFFORD, CAPT., M.C., AND R. L. HULLINGHORST, LT. COL., M.C.,
SAN FRANCISCO, CALIF.

(From the Letterman General Hospital)

FEW cases of poliomyelitis in pregnancy have been completely reported. Most reports are of isolated cases or of small series.¹⁻⁴⁴ The most extensive review of these was made by Weaver and Steiner⁴⁵ in 1944, covering 75 cases. The following case is the first one reported with virus and histologic studies on both mother and fetus. The accompanying review summarizes all available case reports of poliomyelitis in pregnancy in the American, English, French, German, and Scandinavian literature.

Case Summary

Patient was a 24-year-old para i, grav. ii, in the eighth month of pregnancy. Prenatal course, as well as entire past history, was not remarkable. Six days before entry into the hospital she became nauseated and vomited. During the following five days she experienced malaise, weakness, anorexia, and constipation. She continued to vomit sporadically. There were aches in her back, neck, sides, and legs, and a persistent temperature of 100.5° F. At time of entry, June 18, 1946, temperature was 102.2° F., pulse 130, respirations 26, blood pressure 115/75. Patient was weak and nervous. Neurological and physical examinations were negative. Red blood cells, 3.4 million, hemoglobin, 10.5 Gm., white blood cells, 11,400, with normal differential. Urine showed 2+ albumin, many fine and coarse granular casts, and 2 to 4 pus cells per high dry field. Fetal heart sounds were present.

Patient was given intravenous fluids, morphine for pain, and oxygen for dyspnea. On the third day after entry there was marked weakness, moderate nuchal rigidity, paralysis of internal rectus muscle of the right eye, and nystagmus of the left eye to lateral gaze. Water was regurgitated through the nose, and breathing was shallow. Spinal puncture showed a pressure of 360 mm. of water, with 200 cells, mostly lymphocytes. Penicillin and prostigmine were started. Fetal heart sounds were still present. Within sixteen hours the weakness became more marked, air hunger was present, and patient would not respond to external stimuli. The extremities were flaccid. Heart sounds were good. Patient was placed in a respirator, and nasal oxygen continued. Within 20 minutes the posterior pharynx began to fill with mucus; patient became cyanotic and pulse could not be felt. She was pronounced dead 62 hours after admission.

Autopsy Findings

Autopsy performed two hours after death revealed signs of asphyxia, a pregnancy of eight months, and evidence of an encephalomyelitis. The cerebrospinal fluid was cloudy, and the leptomeninges were markedly congested. Scattered areas of congestion were present throughout the subcortical white matter, basal ganglia, and brain stem. The anterior horns of the spinal cord were swollen and congested. Microscopically, there was typical perivascular infiltration by mononuclears and occasional neutrophilic polymorphonuclears. In focal areas in the parietal cortex, basal ganglia, cerebellum, pons, and medulla, neurons showed swollen cell bodies, clumping of Nissl substance, loss of nuclear detail, satellitosis, and neuronophagia. Similar changes were present in the spinal cord, particularly in the region of the anterior horns.

Examination of the gravid uterus revealed a well-developed and well-nourished fetus weighing 2750 Gm. and measuring 48 cm. in crown-heel length. Maceration was not present. Scattered petechiae of serosal surfaces were the only gross abnormalities. Multiple sections of cerebrum, cerebellum, brain stem, and spinal cord revealed no abnormalities microscopically.

Through the courtesy of the Hooper Foundation of the University of California, virus studies of brain and spinal cord of both mother and fetus were performed. Poliomyelitis virus was isolated from the maternal tissue, but could not be demonstrated in the fetus.

Discussion

An analysis of 170 cases (case reported here included) of poliomyelitis in pregnancy was made. This includes practically all of the cases reported, with the exception of those analyzed by Aycock⁴⁶ only with regard to the stage of pregnancy and sex of fetus. Many of the cases included here have been reviewed in part in previous reports.

In 150 instances, the age of the mother is stated. In Fig. 1, with consideration of the sources from which the material is drawn, it is shown that there is no significant variation from the expected normal age incidence of pregnancy.

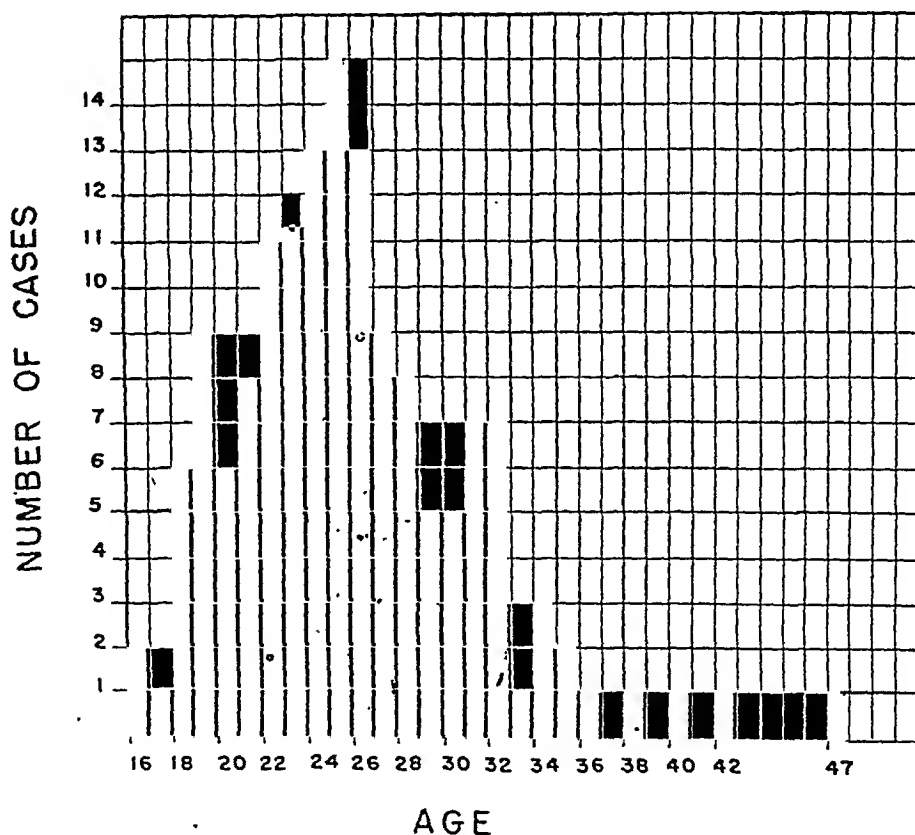


Fig. 1.—Age distribution.

There are 56 instances in which the number of previous pregnancies is stated. Fig. 2 shows no significant variation from the expected normal, the majority being cases of first or second pregnancy.

In 1941, Aycock²⁷ stated that data collected by him from 56 cases suggested a slight tendency for poliomyelitis to occur more frequently in the last trimester. Weaver and Steiner⁴⁵ in their review of 75 cases showed fewer cases to occur in the first trimester. Their animal experiments likewise supported this view. In

1946, Aycock⁴⁶ stated that there appeared to be no tendency for poliomyelitis to occur at any specific period of pregnancy. In 166 of the cases reviewed here, the stage of pregnancy is listed. Analysis shows the following incidence:

First trimester	22 per cent
Second trimester	35 per cent
Third trimester	40 per cent
Post partum	3 per cent

This again suggests increased resistance in the first trimester. However, analysis by months reveals that the incidence in the third month is second only to that in the ninth month (Fig. 3). Apparently the low incidence recorded in the first trimester is due to incomplete reporting, or failure to recognize pregnancy in the first two months.

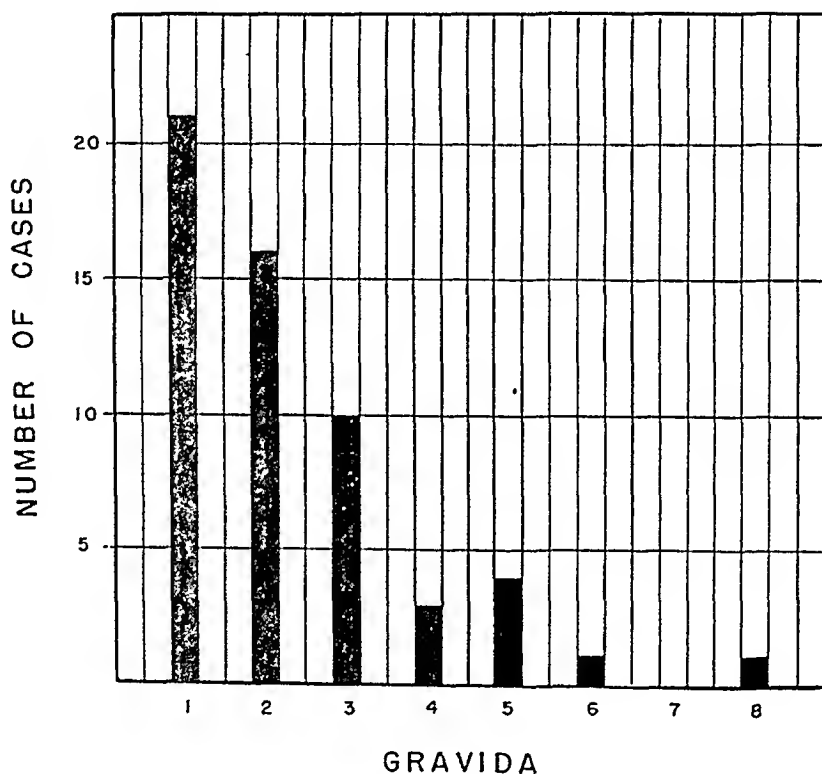


Fig. 2.—Number of pregnancies.

It is now recognized that epidemics vary as to attack rate, incidence and severity of paralysis, and type of paralysis. As early as 1913 Wiekman⁹ estimated that 25 to 56 per cent of cases of poliomyelitis were nonparalytic, and 6 per cent were bulbar in type. Analyses of recent epidemics show great variation around these general estimates.⁴⁷⁻⁴⁹ Most data, however, disregard sex and age, and do not allow for comparison with the cases reviewed here. Of these 170 cases, the following is the incidence of type involvement:

Bulbar	23 per cent
Spinal	37 per cent
Aparalytic	8 per cent
Not reported	32 per cent

It is felt that the 23 per cent incidence of bulbar paralysis here is probably higher than the average incidence of such involvement in adult females in epidemics of poliomyelitis.

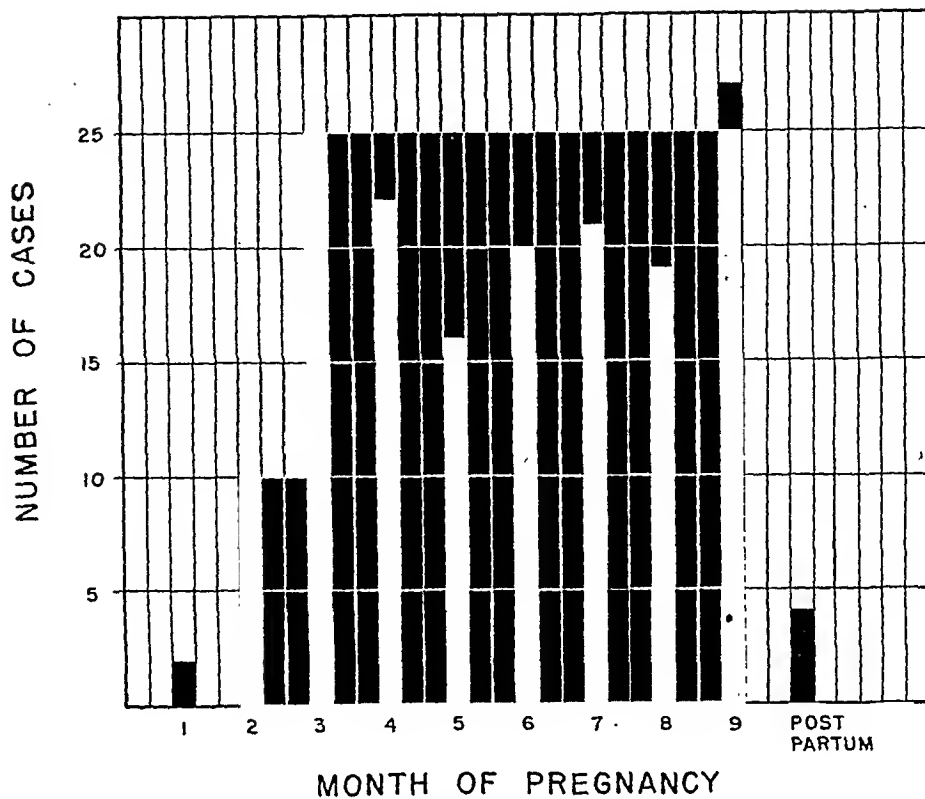


Fig. 3.—Stage of pregnancy

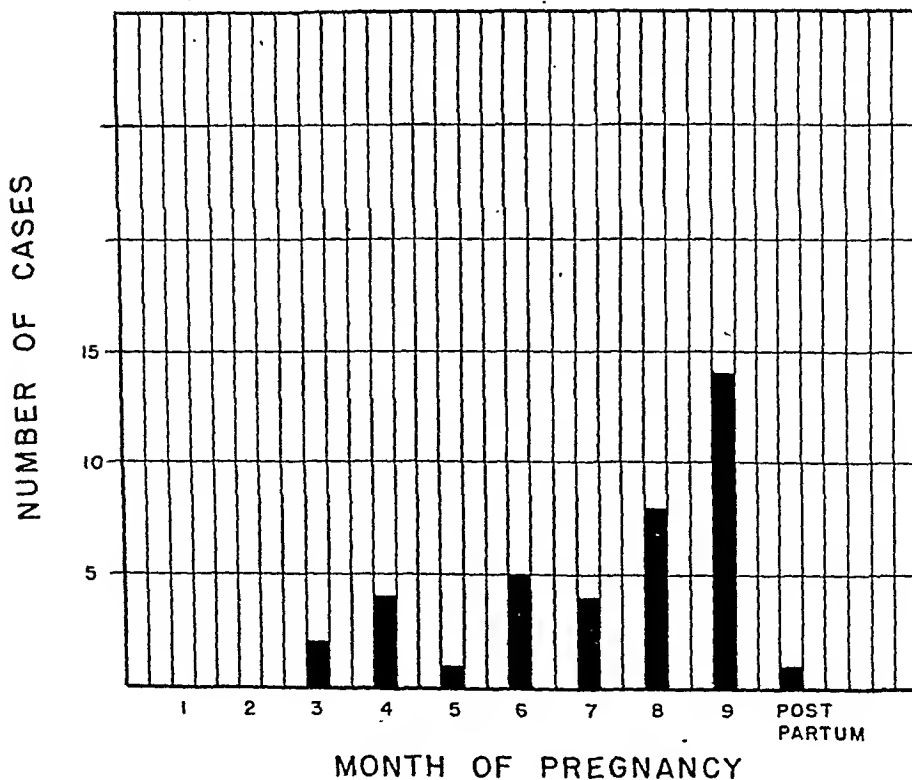


Fig. 4.—Bulbar cases by stages of pregnancy.

Investigation of the 39 bulbar cases shows a marked increase in incidence in the last two months of pregnancy (Fig. 4). An explanation of this fact may lie in the increased mechanical difficulty of respiration normally found in pregnancy. This extra load may either make latent cases of bulbar paralysis apparent or increase the respiratory difficulty in frank bulbar cases. Strauss and Bluestone⁴³ report a case of a pregnant woman maintained in a respirator from the fifth to the eighth month of pregnancy. With the progress of the pregnancy, it was noted that both the rate and pressure of the respirator had to be increased to compensate for the increasing resistance to diaphragmatic motion produced by the enlarging uterus.

Fetal deaths are reported in 45 instances (26 per cent of cases) and show the following groupings:

1. Type of Maternal Paralysis	
Spinal	15
Bulbar	14
Aparalytic	4
Not reported	12
2. Type of Fetal Death	
Spontaneous abortion	13
Therapeutic abortion	1
Prematurity	3
Stillbirth	7
Cesarean section	6
Undelivered (maternal death)	14
Not reported	1

Nine of the 13 abortions occurred in cases of spinal type paralysis and 3 in aparalytic cases. In one case, the type of paralysis is not reported. Of the 7 premature births, 3 occurred in cases of spinal type paralysis, 1 in bulbar, and 3 in cases in which the type of paralysis is unreported. None of the cases showing bulbar involvement aborted. Only one bulbar case delivered prematurely.

No maternal deaths are reported associated with premature births. This, together with the low incidence of premature births in bulbar cases, suggests that precipitous delivery seldom occurs during an anoxic or agonal period.

Thirty-two maternal deaths, a mortality of 19 per cent, are reported. Of these, 26 showed bulbar involvement, and, in the other 6 cases, the type of involvement is not stated. In the first group, cesarean section (7 cases) may have caused or contributed to death. In the second group, with unreported type of involvement, only one cesarean section was done. The other five deaths were most likely due to respiratory paralysis.

According to numerous authors,^{14, 21, 25, 35} respiratory paralysis in the latter months of pregnancy is an indication for cesarean section, not only to obtain a viable child, but to relieve the respiratory distress of the mother. Yet there have been no series of cases of this kind published. In this series, there are 17 cesarean sections reported. The type paralysis, and effect on mother and fetus are as follows:

TYPE PARALYSIS		MATERNAL DEATH	FETAL DEATH
Spinal	2	0	1
Bulbar	9	7	2
Not reported	6	1	3
	—	—	—
	17	8	6

All 6 deaths of issue occurred in the fifth to eighth month of gestation. All 7 of the babies delivered by cesarean section during the ninth month and 2 of the 4 delivered during the eighth month lived.

Several authors^{20, 50-54} have recorded postnatal findings which are very questionably poliomyelitic in nature, and in which there is no definite proof of poliomyelitis being transmitted from mother to fetus in utero. However, poliomyelitis may be acquired by the newborn infant. Bierman and Piszczek³⁷ report a case of poliomyelitis in an 11-day-old infant, the mother having shown signs of poliomyelitis twenty-four hours antepartum. Aycock²⁷ reports the apparent transmission of poliomyelitis, contracted by the mother at term, to a 12-day-old infant. A case reported by Palmstierna³⁹ is particularly worthy of note. The mother died from poliomyelitis during cesarean section. The apparently normal child showed signs and spinal fluid findings of poliomyelitis twelve days postpartum. Since the child had no contact with the mother, this case is advanced by the author as a possible example of intrauterine transmission of the disease. However, the late development of poliomyelitis in the child suggests an extrauterine transmission.

In all the cases studied in this review, no definite clinical evidence of intrauterine transmission of poliomyelitis has been found. This does not necessarily mean that the placenta acts as a barrier against such transmission. In man, the poliomyelitis virus has been isolated from the blood stream in only one instance.⁵⁵ Hence the placenta is rarely, if ever, exposed.

Careful postmortem studies of both mother and baby have been reported in only a few instances. Harmon and Hoyne³⁴ reported a case in which virus studies on the spinal cord of the fetus were negative. In autopsy on two undelivered maternal fatalities, Waaler⁴² found no histologic evidence of poliomyelitis in the central nervous systems of the fetuses. The case presented here showed maternal poliomyelitis by histologic and virologic studies. There was no evidence of poliomyelitis in the fetus demonstrable by either means.

Summary and Conclusions

1. An analysis of 170 cases of poliomyelitis in pregnancy is presented.
2. The age, number of previous pregnancies, and stage of pregnancy do not appear to be factors in the susceptibility of the pregnant woman to poliomyelitis.
3. Bulbar type of paralysis shows an incidence of 23 per cent. The incidence of bulbar involvement is increased in the last trimester of pregnancy.
4. Bulbar poliomyelitis shows no tendency to result in abortion or premature birth, or to cause precipitous delivery.
5. A maternal mortality of 19 per cent and a fetal mortality of 23 per cent is reported. One-third of the fetal deaths were intrauterine and undelivered, associated with maternal death.
6. Cesarean section offers a good opportunity to obtain a viable child, when death of mother is imminent.
7. Poliomyelitis may be transmitted to the newborn, but there is no definite clinical, histologic, or virologic evidence of its transmission in utero.

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Discussion

DR. HOUSTON EVERETT, Baltimore, Md.—The method of approach which Dr. Huffman has adopted, namely the construction of wax models from serial microscopic sections, is one which among embryologists and students of the details of the more minute anatomic structures is considered practically infallible. I believe, therefore, that we may accept his work as the last word in the anatomy of these glands or ducts associated with the female urethra.

Previously there has been considerable confusion upon this subject, and eminent authorities have differed widely, some claiming that, aside from Skene's glands, there are no glands worthy of the name associated with the female urethra. Others have described numerous paraurethral glands which they have considered as homologous to the male prostate. If I interpret Dr. Huffman's findings correctly, they result in some approximation between these previously considered opposite points of view. In other words, most of the glands he described might be considered as part of the Skene's duct system, as their main ducts tend to enter the urethra in its lower portion, but on the other hand this makes of this system a considerably more elaborate and complex one than the two paraurethral ducts originally described by Alexander Skene.

From the clinical point of view, gynecologic interest in the paraurethral glands was chiefly concerned with the fact that Skene's ducts often became involved in gonorrheal infections. This usually resulted in a chronic gonorrheal urethritis which was intractable to treatment until the focus of infection in these tiny glands was eradicated. The modern chemotherapeutic and antibiotic methods of treating gonorrhea have gone far in reducing the incidence of this phase of the disease. However, it is quite probable that deep-seated infection of a nonspecific nature in these glands may play an important role in the so-called nonspecific or granular urethritides, which often prove to be an exceedingly difficult therapeutic problem. That these glands are important factors in the production of suburethral abscesses, cysts, and diverticula, it seems to me is hardly open to doubt.

I rather wish that Dr. Huffman had not found it so convenient to apply the term *female prostate* to the group of glands under consideration. This is not a new concept, and this anatomical concept in the past has led, upon the part of certain eminent urologists, to an overly enthusiastic adoption of the clinical concept of *female prostatism*. This idea in turn has resulted in the too frequent use of the cautery punch or resectoscope on the female vesical orifice. Upon the basis of what I believe would be considered a rather large experience in dealing with female urological patients, I am thoroughly convinced that obstructions at the vesical neck sufficient to produce residual urine or retention of urine rarely occur in the female from causes in any way simulating prostatism in the male. Furthermore, I am convinced that the use of the cautery punch or resectoscope on the vesical neck of the female carries with it certain dangers of intractable sphincter incompetence or even vesicovaginal fistula. As it usually falls to the lot of the gynecologist to correct such defects, they are probably much more seriously appreciated by the gynecologist with an adequate urological experience than by a urologist with little or no experience in gynecology.

DR. ARTHUR H. CURTIS, Chicago, Ill.—Despite the fact that I went over Dr. Huffman's paper with painstaking care and approved of it as it was to be presented, I am heartily in accord with Dr. Everett's objection to calling this glandlike tissue the female prostate. Anatomically, it is probably analogous, but "female prostate" is an unfortunate name to use. There must be no implications which may tempt clinicians to resort to surgical extirpation.

DR. HUFFMAN (Closing).—Dr. Everett and Dr. Curtis have pointed out the error of my ways in using the term "female prostate." I think that perhaps I was guilty of placing too much emphasis on the embryology of the paraurethral ducts and glands. They are of course homologous with the prostate, but I can see where it would perhaps be better not to use the term "female prostate," at least in clinical medicine.

reticulocytes 0.4 per cent; clotting time: (1) 10 minutes, (2) 8 minutes; bleeding time $1\frac{3}{4}$ minutes; glucose tolerance, fasting, 88 mg., one-half hour, 159 mg., one and one-half hours 198 mg., two hours, 88 mg.; blood Hinton negative.

Abnormal bleeding had begun July 3, 1935, and became so severe that on July eighth a curettement was necessary. (Fig. 1.) Endometrial biopsy showed an estrogen phase. Following curettement (unlike metropathia hemorrhagica) the patient continued to bleed, and bled steadily through July, August, and September, until the third of October, when exploration revealed varicosities of the left broad ligament only. Convalescence from operation was complicated by pain in shoulder and neck and gross hematuria, possibly due to a renal infarct.

Following this operation, she continued to bleed for ten days to October fourteenth. Then, on the eighth of November, she started to bleed again and bled constantly to Feb. 21, 1936. From November thirtieth to December fourth, she received 2,500 units of Antophysin, continued to bleed, and two biopsies, ten and thirteen days following, showed an estrogen type of endometrium. At the time of the biopsies, she was given Antophysin, 2,500 units, and, twenty days after that, still bleeding, had a progesterone type of reaction on endometrial biopsy. Following that, she continued bleeding for over a month, in spite of six doses of Prephysin (anterior pituitary extract) and an additional 2,500 units of Antophysin, this bleeding necessitating a curettement again on February fourteenth. This endometrial specimen showed estrogen influence. The bleeding continued for eight days more, and, on the tenth day following curettement, a secretory type of endometrium was obtained for the second time. This ovulation may have been brought about by curettage, as occasionally happens, but, in spite of this apparently normal period, abnormal bleeding recommenced and continued through the month of March. At the end of March, another biopsy, taken when the patient should have ovulated, showed an estrogen type of endometrium. She was given more Antophysin, continued bleeding, and two more biopsies, nine days apart, at the end of April, showed estrogen phases.

At the beginning of May, she was treated daily with 1 mg. of Proluton, now considered an insufficient dosage, and, at biopsy on the fourth day during the treatment, showed, nevertheless, a secretory endometrium. Her catamenia started five days after this biopsy, and, on the third day of the period, at biopsy, no tissue could be obtained, and the patient's period continued for fifteen days. A Lipiodol examination showed no abnormality of the uterus or tubes. At this point, almost continuous bleeding now having persisted for nine months, the patient and the doctors became discouraged, and it was felt that the uterus should be removed.

It is obvious that a sufficient number of biopsies had not been taken to prove that the patient did not ovulate regularly, but we had proof on two occasions that, in spite of ovulation, her flowing continued abnormally after the secretory phase must have been past. Such bleeding is not typical of the usual metropathia hemorrhagica cases. This fact suggested the advisability of a psychiatric consultation, preliminary to hysterectomy. It is significant that, when the patient was informed that hysterectomy was to be postponed, mild depression and hysterical symptoms for the first time became apparent.

The patient first discussed her personal problems with a physician on May 20, 1936. (Fig. 1.*) Three days later, on May 23, bleeding had ceased. She had normal periods in June and July. The August period was interrupted, but of normal duration. Periods of mild prolonged bleeding then recurred from September, 1936, through April, 1937 (see discussion). For nine years thereafter (May, 1937, to April, 1946) the catamenia have been essentially normal.

Discussion

Menstruation implies cyclic pituitary activity with a chain of consequences, including follicle growth, ovulation, corpus luteum formation, development of a secretory endometrium, and subsequent shedding of this endometrium with bleeding. We know that, given an endometrium under the influence of estrogen, if this hormone be withdrawn, bleeding will occur. Anovulatory bleed-

MENSTRUAL DYSFUNCTION DUE TO EMOTIONAL FACTORS

MAURICE FREMONT-SMITH, M.D., F.A.C.S., AND JOE V. MEIGS, M.D., F.A.C.S.,
BOSTON, MASS.

(From the Vincent Memorial Hospital [the Gynecologic Service of the Massachusetts General Hospital] and the Department of Gynecology of the Harvard Medical School)

A MENORRHEA and abnormal bleeding constitute two of the most frequently encountered symptoms in gynecologic practice. Evidence has accumulated within the past decade to suggest that menstrual abnormalities may be caused not only by organic, but also by emotional factors, and that, when the latter are primary, surgery and endocrine treatment are often useless. In such cases, therapy must be directed to the cause rather than to the symptoms; in other words, the person presenting the abnormality of menstruation, rather than her organs, becomes the object of therapy.

Ten years ago, a young woman whose persistent metrorrhagia apparently warranted hysterectomy was seen by one of us. However, before operation was undertaken, because emotional upset was evident, an internist was called in consultation. After three hours of conversation, during which anxiety was uncovered and to some extent relieved, the uterine bleeding, which had persisted almost continuously for nine months, ceased. No operation was performed. The patient had no significant menstrual difficulty thereafter, and a follow-up of over nine years constitutes the basis for this report.

In the light of this experience, it has been thought important to review the physiology of menstruation, with emphasis upon those menstrual abnormalities which may be caused by anxiety or other emotional disturbance. In order to avoid destructive surgery in unsuitable cases, the physician must be able to consider in his diagnosis all possible causes of abnormal uterine bleeding, the psychology, as well as the "functional," and the organic.

Case Report

A twenty-six-year-old single white woman was seen Dec. 12, 1935, for uterine bleeding, then of five months' duration. The family and past history were noncontributory. The periods had started at thirteen, and had always been profuse and irregular. The patient bruised easily with trauma, and had bled once for twenty-four hours, following a dental extraction. There was no history of purpura. The diet was adequate, including fruit, vegetables, and meat. Thyroid medication had been begun in 1932 and was continued during the entire period of observation.

Examination showed a girl of dark complexion and normal hair distribution. No petechiae. Tourniquet test negative. Ocular fundi negative, visual fields full. Breasts virginal, shotty, suggesting cystic disease. Blood pressure 135/80, heart and lungs normal. Abdomen, midline scar, spleen not felt. Pelvic, clitoris normal, fundus forward, endocervix 2.5 cm., whole uterus 8 cm. Unclothed blood coming from a normal external os. Ovaries palpable, normal size.

X-rays showed a small sella with heavy clinoids, thought to be "within normal limits." Metabolism minus 10 per cent. Urine normal. Red Blood count 4.5, white blood count 6.8, hemoglobin 104 per cent (Sahli), platelets high normal; differential leucocyte count normal,

ing is of this type. If the endometrium has been previously exposed to both estrogen and progesterone, the withdrawal of the latter hormone alone will result in bleeding. Normal cyclic menstruation involves this mechanism.

Markee¹ studying endometrial transplants in the anterior chamber of the eye, found that, in both ovulatory and anovulatory cycles, there occurs a marked decrease in endometrial volume two to six days before bleeding. This regression, he believes, results from estrogen deprivation. As a result of this tissue loss, buckling and twisting of the coiled arteries take place, with consequent arterial stasis and endometrial necrosis. Just before bleeding commences, there is seen a second vascular change which Markee describes as follows: "Four to twenty-four hours before the onset of menstrual bleeding there occurs vasoconstriction of the coiled arteries . . . which persists throughout the period of menstrual bleeding, being interrupted in individual vessels only for short periods. It is during these periods of relaxation that menstrual bleeding occurs."

The cause of the vasoconstriction is not known. Smith and Smith² have found in menstrual blood a toxic protein believed to result from the products of endometrial catabolism. They say, "the primary cause of endometrial catabolism is certainly hormone deprivation, and the final precipitating factor resulting in flow . . . may well be the above-described atypical euglobulin whose pathological effect is characterized by vasoconstriction, increased capillary permeability, edema, hemorrhage, and necrosis." Markee³ is in substantial agreement with this hypothesis, postulating the presence of "some substance similar to the necrosin of V. Menkin"—to account for alternating vasoconstriction and hemorrhage.

In metropathia hemorrhagica, bleeding proceeds from a proliferative endometrium, often hyperplastic because of prolonged estrogen stimulation, uninterrupted by ovulation and consequent progesterone influence.⁴ In this condition, the endometrium may outgrow the available supply of estrogen, a consequent relative estrogen deficit resulting, with effects comparable to those following estrogen withdrawal. In metropathia, bleeding ceases following the removal of the proliferative endometrium surgically (by curettage), or medically, by carrying the endometrium into an early secretory phase by means of injections of progesterone, after which it is shed spontaneously.

The cause of the cyclic activity of the pituitary essential to normal ovarian function is unknown. Smith and Smith⁴ suggest that the toxin, which, they believe, results from the products of endometrial catabolism, may function as a physiologic stimulus to pituitary activity. They suggest that, since more "toxin" is liberated from secretory than from proliferative endometrium, in metropathia insufficient pituitary stimulation occurs, with consequent low follicle-stimulating hormone production and failure of ovulation. Thus a vicious circle would be set up.

A number of factors are recognized which may interfere with the activity of the pituitary, with consequent disturbance to the menstrual cycle. Thus, with atrophy or destruction of the anterior pituitary (Simmonds' disease,

*Whenever ovulation is absent over long periods, if estrogen production persists, metropathia may result. In young women, an occasional cause of failure to ovulate is the presence of a congenitally thickened ovarian capsule. Here, mechanical interference with follicle rupture is present. In women near the menopause, follicles may fail to respond (by growth and rupture) to a normal or even increased pituitary stimulus. In either case, long-continued bleeding (metropathia) may result.

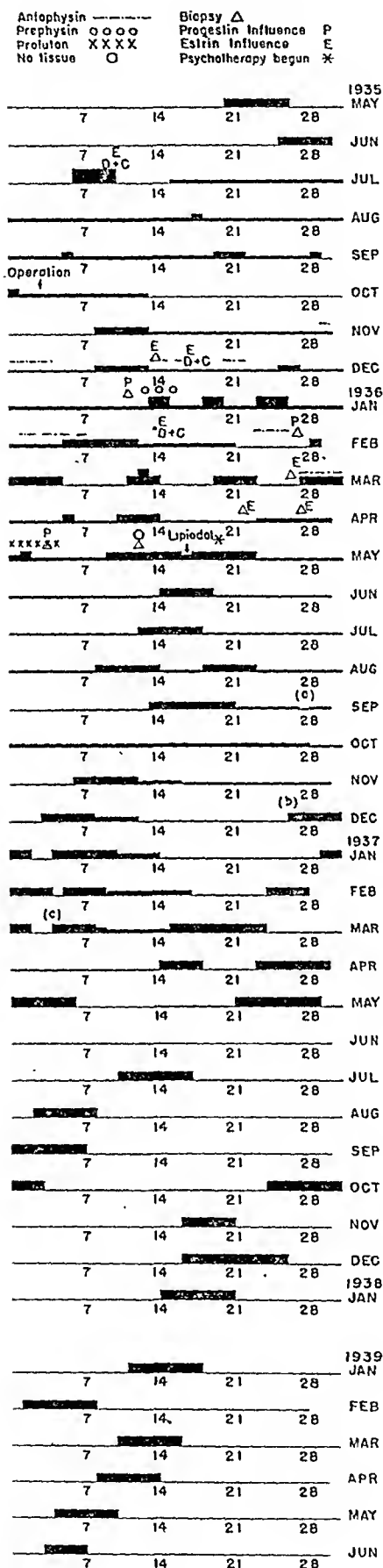


Fig. 1.

these amenorrheic women completely lack luteinizing hormone. Absence of the hypothalamic stimulus which normally brings about the pituitary release of luteinizing hormone is suggested as the probable reason for this type of amenorrhea. Such hypothalamic inhibition is believed to result from emotional factors. Estrogen production and normal cyclic periods usually return following relief of emotional tension.

A number of clinical reports⁸⁻¹¹ have appeared, indicating a relation between psychic disturbance and abnormal menstrual function. Delay or suppression of menses as the result of hypnosis or following "suggestion" has been described (Novak and Harnik, and Miller).

It is, therefore, probable that emotion, by causing changes in endocrine balance, may bring about either amenorrhea or uterine bleeding. A more direct neurogenic control of uterine bleeding may also exist. Soskin et al.¹² have shown that, in certain delayed cycles in otherwise normally menstruating women, bleeding may be induced by the injection of prostigmine. During pregnancy, injection of the drug is not followed by bleeding, nor does such bleeding follow the use of prostigmine in amenorrhea due to gross endocrine disturbance. His observation suggests, since the autonomic nervous system is closely associated with the emotional centers, that integration between psychic activity and uterine physiology may be mediated, not only through hormonal changes, but also by direct neurogenic control of endometrial vascularity.

The significance of the emotions appears to be clear-cut in the case here reported. In the course of the second interview, it was learned that the onset of excessive flow had coincided with a period of acute anxiety and indecision relative to marriage. At that moment, the patient had become convinced that her life problem was insoluble, felt doubtful of her competence as a person, and considered herself a failure. Guilt feelings, taking origin from false parental attitudes and childhood experiences, were expressed and modified by discussion. The patient was "desensitized" to certain concepts.

It is probably significant that a subsequent onset of abnormal bleeding (see Fig. 1, a) began during the week before she started a new and difficult job, when fear of failure and sense of personal inadequacy again became acute. Another period of relatively prolonged bleeding (b) occurred when she again "fell in love"; still another, (c) when she was repudiated by the man who "decided to marry the other girl."

In the nine years subsequent to the termination of psychiatric discussions of a simple type, the periods have been more regular than at any time in the patient's menstrual life. There has been no recurrence of prolonged bleeding. The patient has grown in self-confidence and independence. Responsible positions have been successfully held over this nine-year period.

Conclusion

A woman, aged twenty-six, with uterine bleeding of many months' duration, was studied at both somatic and psychic levels. Despite ovulation (two secretory endometrial biopsies), bleeding continued. Organic cause for metrorrhagia was eliminated. Endocrine treatment and minor surgery were both ineffective. Bleeding terminated after three hours of discussion, during which guilt and anxiety were partially relieved.

Sheehan's disease), by interference with the hypothalamic-pituitary pathways (suprasellar cyst), or with functional inhibition of the basophile cells by estrogens (granulosa-cell tumor, estrogen therapy) or by androgens (arrhenoblastoma), follicle-stimulating hormone falls to low levels, ovulation does not occur, and cyclic bleeding ceases. Grave systemic disease, severe anemia, protein starvation, sudden increases in body weight, and hyperthyroidism may each cause irregularity or disappearance of the menses.

Emotion is known to have an important influence upon menstruation. Markee,⁵ observing the arrest of bleeding in endometrial transplants during the late phase of menstruation, says, "Fright at this stage causes, within fifteen to twenty-five seconds, reopening of the arteriole which, for five to fifteen seconds, delivers blood that promptly clots." Fear (as of pregnancy) may delay or suppress a menstrual period. The mechanism of such inhibition is not well understood. Once ovulation has occurred, it would seem that bleeding must generally result from the involution of the corpus luteum about fourteen days later.

According to Loeser,⁶ temporary arrest of endometrial development may occur as a result of psychic trauma, the endometrium, in whatever phase, remaining in statu quo following the emotional shock.

Loeser studied four women with histories of regular menstruation, each of whom experienced an "emotional shock" during the aerial bombardment of London. Three were exposed to nearby bomb explosions, the fourth developed acute anxiety concerning a possible pregnancy. In each case, an expected menstrual period was missed. Loeser, obtaining endometrial biopsies during the amenorrheic stage, sent the specimens to Emil Novak, who knew the dates of neither the last menstruation nor of the biopsy. In each case, Loeser says "biopsy specimens showed an endometrium at the stage of development it would normally have reached at the time of the shock, suggesting that the shock caused an immediate arrest of development by interruption of release of the proper (pituitary) hormones." Two biopsy specimens showed proliferative endometrium many days after ovulation should have occurred. Ovulation may well have been delayed in these cases through hypothalamic disturbance (as in Albright's cases, see below). More difficult to explain are two biopsies which were interpreted as early secretory endometrium. Loeser believes this indicates that, if an emotional shock be experienced in the postovulatory phase, the endometrium may neither develop nor regress, but remain static and unchanged over a period of days.*

Young women under the stress of college or undergoing the strain of nurses' training often fail to menstruate over a space of several months. Such women have been studied by Klinefelter, Albright, and Griswold,⁷ who find, in many cases, complete absence of active estrogen (no bleeding after progesterone withdrawal, atrophic endometrium on biopsy, atrophic vaginal smears) in spite of a normal follicle-stimulating hormone urinary assay. These cases fall, therefore, neither into the group of pituitary failure (low F.S.H.), nor of ovarian failure (menopause, high F.S.H.). As the ovary will not produce active estrogen when stimulated by F.S.H. alone, but needs also a trace of luteinizing hormone (Greep) in order to secrete active estrogen, Albright suggests that

*If the endometrium was, in fact, postovulatory, it would seem more reasonable to postulate that an ovulation, inhibited by the emotional disturbance, had occurred two or three days before the biopsy specimen was obtained. This would better explain an early secretory postovulatory endometrium could persist without change for twenty-four days. In any case, Loeser's observations are of interest and should be repeated wherever cases of delayed menstruation due to anxiety are observed.

UTERINE SUSPENSION*

A Report of Results

WILLIAM H. VOGT, JR., M.D., ROY V. BOEDEKER, M.D., AND
GUILLERMO LOPEZ, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, St. Louis University School of Medicine)

THIS is not a clinical study of the causes of success or failure of uterine suspensions. It is simply a review of our own results with the procedure, as a method of relieving a variety of feminine complaints associated with simple or complicated retroversion of the uterus.

So many similar series have been reported with statistical evidence to support the procedures recommended, that one ought to be able to consider the subject a matter of sound and well-established principles.

Although the 220 operations herewith presented were done by different members of the staff of the University Hospital over a ten-year period, the indications and techniques conform, in general, to the principles thus established. Nevertheless, we have personally felt that the operation is a much abused procedure, and, to prove or disprove our theory, undertook a rather painstaking search of the records, paying particular attention to the postoperative reports of the patients themselves. In evaluating the degree of success or failure of any elective surgical operation, we are always confronted with the human equation. However, since subjective symptomatology is usually a primary consideration in determining the need for surgery, the relief or continuation of the symptoms postoperatively should be an adequate criterion of success or failure.

For simplicity, we have classified the patients, as regards end results, into one of four groups, namely: (1) those who were entirely free of all symptoms as "Excellent"; (2) those who were relieved of some, but not all, of their complaints as "Fair"; (3) those who complained just as bitterly or more so of their various symptoms as "Poor," and, finally, (4) those in which the uterus was found retrodisplaced postoperatively as "Failures."

Since all authorities agree that no single operation is universally applicable, the following general principles guided the choice of procedure:

If the retrodisplacement was due to childbirth, the round ligament suspension was associated with repair of the pelvic floor and, in certain instances, reconstruction of the sacral ligaments.

If the retrodisplacement was due to adnexal disease, some type of round ligament suspension which utilized the heavy medial muscular portion of the ligament was used. The Baldy-Webster technique was employed as a method of correcting associated prolapsed ovaries.

The following table illustrates the type operation selected by the various surgeons:

*Presented at a meeting of the St. Louis Gynecological Society, Oct. 9, 1947.

Proof is lacking that anxiety caused, or that relief from anxiety terminated, the metrorrhagia. The onset of the bleeding, however, coincided with a phase of acute anxiety. The patient bled almost constantly for nine months, during which time no solution of her life problem was evident to her. The bleeding itself, however, constituted a partial solution, as hysterectomy would also, in part, have solved her problem. She was subsequently followed for nine years, during which no abnormal bleeding has occurred.

It is concluded that cases of prolonged bleeding in young women should be studied at both somatic and emotional levels before destructive major surgery is undertaken.

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The following operations were done at the same time the uterus was suspended:

TABLE IV. ASSOCIATED OPERATIONS

	NUMBER OF CASES
Sturmdorf	31
Tracheloplasty	9
Cauterization of cervix	6
Conization of cervix	1
Myomeectomy	2
Colporrhaphy	26
Salpingo-oophorectomy	16
Dilatation and curettage	63
Adhesiolysis	8
Appendectomy	12
	<hr/> 174

Results

In categorizing our results, 52 cases were deleted because of inadequate follow-up or failure of the recorder to make a definite statement regarding the relief of symptoms. Upon the basis of the classification outlined above, results were as follows:

TABLE V. POSTOPERATIVE RESULTS

COMPLICATED: 116 CASES			UNCOMPLICATED: 52 CASES		
EXTENT OF RELIEF	NO. OF CASES	PERCENT-AGE	EXTENT OF RELIEF	NO. OF CASES	PERCENT-AGE
Excellent	36	31%	Excellent	13	25%
Fair	31	27%	Fair	2	3.9%
Poor	47	40%	Poor	37	71%
Failures	2	1.8%	Failures	0	0%

Comment

It is evident from the above that almost three-fourths of the patients of the uncomplicated group failed to attain satisfactory results from their operations. Since the therapy is far from a lifesaving procedure and, certainly, not entirely without hazard, it would seem that these results are definitely unsatisfactory. The associated surgical treatment given the complicated group can probably be credited for the better results for that group, in which only 40 per cent failed to attain satisfactory results. To illustrate that this procedure is not innocuous, there were, following surgical correction, three cases of thrombophlebitis, two of wound infections, and two patients developed intestinal obstruction in the course of the follow-up period.

Cursory consideration of these results seems to lead to the conclusion that the majority of retroversion operations are unnecessary. More deliberate study of the many factors involved, the majority of which cannot be outlined in statistical tables, has led us to the more constructive viewpoint of Dannreuther: "(a) Retrodisplacements of the uterus per se do not cause symptoms. (b) The concealed complication in cases of replaceable displacement causing symptoms is passive congestion. The true cause of many symptoms credited to a retrodis-

TABLE I. TYPE OF SUSPENSION

	NUMBER OF CASES
Barrett	74
Simpson	68
Baldy-Webster	36
Gilliam	35
Mayo	5
Kocher	2
	<hr/> 220

In an attempt to determine whether the symptoms should be attributed to the retrodisplacement, preliminary trial with pessary in 62 of the 145 movable retrodisplacements produced relief as indicated in Table II.

TABLE II. RELIEF OF SYMPTOMS WITH PESSARY

EXTENT OF RELIEF	NUMBER OF CASES
Excellent	42
Fair	9
Poor	11

With the view of separating cases with coexisting pathology from the simple, uncomplicated retroversions, in the analysis of our results, our series is divided into the two following groups:

Complicated	121
Uncomplicated	99

The following diagnoses were made concomitantly:

TABLE III. TYPE OF COMPLICATION

	NUMBER OF CASES
Menorrhagia	10
Pelvic inflammatory disease	60
Sterility	2
Myomata	2
Cervicitis	47
Relaxed pelvic floor	29
Varices broad ligament	2
Ovarian cyst	5
Habitual abortion	1
Cervical stenosis	1
Visceroptosis	4
	<hr/> 163

CULDOSCOPY, A USEFUL GYNECOLOGIC PROCEDURE*

RICHARD W. TELINDE, M.D., AND FELIX RUTLEDGE, M.D., BALTIMORE, MD.

(From the Gynecological Department of the Johns Hopkins Hospital and University)

FOR a period of years our clinic has been interested in visualizing the pelvic organs in selected cases by means of the peritoneoscope. In many instances we found peritoneoscopy to be a very useful procedure and sufficient additional information often was obtained to save the patient an exploratory laparotomy. In other cases the necessity of surgery became apparent on gaining further information by visualization of the pelvic organs. Useful as peritoneoscopy was, it often left something to be desired. The peritoneoscope entered the abdominal cavity at a considerable distance from the pelvic viscera, and the tip of the instrument often had to find its way through many loops of small intestine before the pelvic region was reached. Not infrequently these loops of bowel were troublesome. Still more troublesome were adhesions from previous operations and at times they made visualization of the pelvic viscera impossible. It occurred to one of us (R. W. T.) that a better and more direct approach to the pelvic organs could be made through the posterior vaginal fornix, and in 1940 such an attempt was made by means of the peritoneoscope with the patient in the lithotomy position. Air was introduced by means of a bulb as in the ordinary transabdominal peritoneoscopy. It was found to be impossible to retain enough air in the peritoneal cavity to prevent the intestines from interfering with visualizing the pelvic viscera. This was due to the fact that the thin vaginal wall failed to grip the peritoneoscope as snugly as the abdominal wall. It remained for Decker to grasp the advantage of the knee-chest posture as a means of sucking air into the abdomen, just as in the air method of cystoscopy. Decker has published four articles on the subject of culdoscopy which are the only ones we have been able to find in the literature.

During the last year we have made frequent use of the culdoscope, and have come to regard it as a valuable diagnostic aid. This paper is a report of our experience in 56 cases.

The Instrument.—Since it is possible that some are not familiar with the culdoscope, the apparatus is pictured in Fig. 1. There is a special trochar with a guard on the sheath about 3 cm. from the tip to prevent introduction of the trochar too far. A valve is attached near the head of the sheath through which CO₂ gas can be introduced into the peritoneal cavity. We have never made use of this, since the results with air have been quite satisfactory. The trochar proper can be fixed in the sheath by means of a special locking device at the head of the sheath. The culdoscope proper consists of a longer metal tube with ocular and objective lenses with a prism to deflect the light so as to

*Presented at the Seventieth Annual Meeting of the American Gynecological Society, the Selwyn Club, Montebello, Quebec, June 17 to 19, 1947.

placement will be found elsewhere. Careful differential diagnosis is of paramount importance. (c) A retrodisplacement may be treated prophylactically, expectantly, palliatively or surgically."

Conclusions

In brief, it is our opinion, as a result of this study, that:

1. We should differentiate coexisting pathology and treat it first. For example, a healed cervicitis may entirely relieve a patient's sideache and backache and obviate the need for suspending the uterus.

2. Laparotomy is indicated without prior trial with pessary when there is need for appendectomy, myomectomy, or salpingo-oophorectomy, or when there are associated pelvic adhesions.

3. Suspension of the uterus is justifiable when preliminary trial with a pessary effects complete relief of symptoms and the patient will not, for reasons of her own, continue to wear the pessary.

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PHENOLSULFONPHTHALEIN AS A TEST FOR THE DETERMINATION OF TUBAL PATENCY

GEORGE SPECK, M.D., ARLINGTON, VA.

THIS is to introduce a test for the determination of tubal patency which is simple, physiologic, and safe.

Phenolsulfonphthalein (PSP)* is instilled into the uterine cavity and, at the end of thirty minutes, the bladder is catheterized. If the urine turns red or pink when alkalinized, the tubes are considered patent; if there is no discoloration, the tubes are considered closed. Based upon animal and human experiments, it was found that PSP is not easily absorbed (if at all) from the normal vaginal mucosa, endometrium, or endosalpinx, but is readily absorbed from the peritoneum. Thus, if the tubes are patent, the PSP will pass from the uterus into the tubes and into the peritoneal cavity where it is absorbed, carried to the kidneys, and excreted, giving rise to a positive test. If the tubes are closed, this will not occur and the test will be negative. The thirty-minute period was chosen for two reasons: (1) PSP was recovered in every instance within twenty-five to thirty minutes when injected into the peritoneal cavity of rabbit does, and (2) if the PSP should be slowly absorbed from the tube or uterus, it would not interfere with the efficiency of the test.

Technique

The vagina and cervix are prepared in the same manner as for an insufflation test or hysterosalpingography. All instruments are sterile. The bladder is emptied and a Graves speculum is inserted into the vagina. The cervix is grasped with a tenaculum and the uterus probed with a uterine sound to determine depth and direction. A cannula (similar to that used with the Jarecho or Rubin apparatus) is filled with PSP solution (12 mg. or 2 c.c. of PSP solution added to 20 c.c. of isotonic saline) and inserted into the uterus, the tip being just above the internal os. The rubber obturator on the cannula fits snugly against the external os and prevents regurgitation. A 20 c.c. syringe containing the remainder of the PSP solution is inserted into the distal end of the cannula and 10 c.c. of the solution is slowly injected into the uterine cavity. The stop-cock at the distal end of the cannula is turned so that there will be no reflux of the PSP solution. The patient is given a glass of water to drink. Ten minutes are allowed to pass before the cannula is removed, for in that time the PSP solution will have passed through the tubes into the peritoneal cavity. A tampon is placed in the vagina and the patient is allowed to rest flat on the table for another twenty minutes. At the end of this time, the bladder is catheterized and the urine collected in a container. Ten per cent sodium hydroxide is added to the urine. If the urine turns pink or red, the tubes are considered patent; if there is no discoloration, closed.

None of the patients seemed to manifest any difficulty during or after the test. Their only complaints were abdominal cramps similar to those found

*Hynson, Westcott and Dunning, Baltimore, Md.

with tubal insufflation or during hysterosalpingography. One patient (No. 6) became pregnant several months after the test.

Sixteen patients were studied and, in each case, the test was found to be accurate in its determination of tubal patency. (Table I.) In ten cases, the tubes were found to be patent as determined by the PSP test. In three of these cases (Nos. 5, 10, and 15) hysterosalpingography was performed and the patency of the tubes substantiated. Case 15 was quite interesting. In 1946, a Pomeroy sterilization was performed. In 1947, when the PSP was done, the results indicated tubal patency which was confirmed by hysterosalpingography.

TABLE I

PATIENT	PRESUMPTIVE CAUSE OF STERILITY	DYE RECOVERED	INSUFFLATION	HYSTERO-SALPINGOGRAPHY	SURGERY
1. M. B.	Oligospermia	Yes			
2. A. L.	Oligospermia	Yes			
3. D. S.	Tubal ligation	No			
4. M. B.	Chronic salpingitis and pyosalpinx	No			Bilateral salpingectomy Hysterectomy
5. M. C.	Oligospermia	Yes		Tubes patent	
6. E. E.	Study incomplete	Yes	Patient became pregnant		several months later
7. M. Z.	Bilateral hydrosalpinx	No		Tubes closed	Right salpingectomy and resection of left tube
	Postoperative	No			
	Postoperative	No	Tubes closed		
8. R. W.	Tubal ligation	No			
9. M. G.	Endocervicitis	Yes		Left tube only patent	
10. M. W.	Huhner tests neg. Sterile since birth of child 15 years before. Probably chronic salpingitis	No			
11. N. B.	Bilateral chronic salpingitis	No			Bilateral resection of tubes
	Postoperative	Yes	Tubes patent		
12. B. K.	Oligospermia	Yes	Tubes patent		
13. R. P.	Oligospermia	Yes			
14. R. M.	Tubal ligation	Yes		Tubes patent	
15. J. P.	Not sterile	Yes			
16. G. D.	Tubal ligation	No			

In seven cases, the tubes were found to be closed as determined by the PSP test. In three of these cases (Nos. 4, 7, and 11) the diagnosis was confirmed by subsequent surgery. In Case 11, a bilateral tubal resection was performed for chronic salpingitis with both fimbriated ends of the tubes closed. Following surgery, the tubes were found to be patent as determined by both PSP and insufflation tests. In the remaining cases, the tubes had been previously ligated and were therefore known to be closed.

Although the number of cases is small, still the accuracy of the test to date has been quite encouraging. Therefore, this preliminary report is being submitted with the hope that others may be struck by the simplicity of the test and the ease with which it can be performed, as well as the economic and safety factors; and, having access to larger groups of patients, that they may be able to substantiate the value of this test. The Rubin insufflation apparatus is not

available to all, and any other method of insufflation using air is so hazardous as to be strongly condemned. The PSP test is neither costly nor dangerous and can be easily performed by all.

I wish to express my appreciation to Dr. William E. Studdiford, Director of the Department of Obstetrics and Gynecology at Bellevue Hospital, New York City, and to the Community Health Center, Alexandria, Virginia, for their cooperation in this study.

Addendum

Since this report was submitted for publication, both Rubin and phenol-sulfonphthalein tubal patency tests have been performed on eight additional patients. In each case, both tests were in agreement in that the tubes were found to be patent.

2806 S. RANDOLPH STREET

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS WITH Rh HAPTEN

JOSEPH LOUGHREY, M.D., F.A.C.S., AND BETTINA B. CARTER, M.S.
PITTSBURGH, PA.

ERYTHROBLASTOSIS fetalis, in its more severe manifestations, still challenges the best of scientific knowledge, and sometimes does not respond to treatment. Many reasonably successful treatments have been advocated. Wiener,¹⁰ Levine,⁸ Davidsohn,⁵ Diamond,⁶ and others have consistently recommended the transfusion of compatible Rh-negative blood into the infant, because the negative blood would not be influenced by the maternal antibodies in the child's blood stream. Wiener,¹¹ and Wallerstein,⁹ among others, have been successful with simultaneous exsanguination transfusions. This procedure removes the major portion of the child's Rh-positive cells and replaces them with Rh-negative ones. It is frequently successful, but presents numerous technical difficulties. Darrow and Chapin⁴ have advocated the use of compatible Rh-positive blood, on the assumption that favorable results are "due in part to the desensitizing action of the transfused cells, as well as to their oxygen-carrying function." In the nonanemic cases with highly active hemopoiesis, some workers, such as Cappell,¹ advocate the withdrawal of some blood preceding transfusion. No method is without serious drawbacks, because of either its inadequacy or the difficulty of timely application. A different approach to the relief of the condition, which might obviate many of the drawbacks of the previous methods of treatment, should be of interest.

We here present the treatment of a case of erythroblastosis neonatorum, of the edematous, nonanemic type, by the application of a new approach to the subject. The treatment consisted of injections of an active fraction from Rh-positive blood, the separation of which was recently reported by one of us.²

Mrs. S., the mother of the baby treated, first came under our observation in 1940, when she was admitted to the hospital in the 36th week of pregnancy, with the diagnosis of abruptio placentae and toxemia of pregnancy. She delivered a macerated male fetus and was transfused with 500 c.c. Group B blood from her husband. She progressed to recovery without difficulty.

The second child, a female, was born in another hospital at the 36th week. A marked icterus was noted on the first pediatric examination. This proved to be progressive. A decision to transfuse the child was made on the second day of life, but she died before the father could be summoned as a donor. A postmortem examination revealed a marked icterus of the tissues, early pulmonary congestion, very marked enlargement and engorgement of the spleen and liver, with marked hemopoietic activity in the stroma of the organs.

The third pregnancy resulted, in February, 1943, again in this hospital, in a girl who is now living and well. Recent examination of her blood showed her to be Group B, Rh negative. This was the last child by the first husband, who was later killed in service. He was Group B, and, by later inference, Rh positive, and heterozygous.

The fourth pregnancy resulted in the erythroblastotic baby girl whose treatment is described. The mother had an uneventful pregnancy, except that her delivery was one month beyond the expected date. During her pregnancy, her blood examination showed she is Group B, Rh negative, and, at 32 weeks, showed positive for anti-Rh sensitization with Race's test and blocking antibodies through a 1:40 dilution. The father was shown to be Group A. His cells were negative to the standard (anti-Rho or anti-D) serum, but were agglutinated by the serum of Mrs. S. Further investigation showed Mr. S. to be an Rh⁺ or cdE type and Mrs. S.' serum contained blocking antibodies of anti-Rho (anti-cDe) specificity and agglutinins against Rh⁺ or cdE. (This work was checked by Dr. Philip Levine.) It is probable that the first husband provided the stimulus for the formation of anti-Rho (anti-D) blocking antibodies.

The child of this fourth pregnancy was delivered at 7:55 A.M. June 8, 1947, after a four-hour labor. The baby was quite edematous, with considerable mucus which could not be entirely relieved by aspiration, so she was placed in an oxygen hood. Examination one hour after delivery showed marked edema, icterus of the skin and sclerae, enlarged liver and spleen, and considerable moisture in the lungs. She was quite lethargic.

Stained smear of cord blood showed 100 immature red cells for every 100 white cells. There were 6,090,000 red cells, 24,000 white cells (corrected count), hemoglobin 18 Gm. Agglutinins against the child's cells and the father's cells were recovered according to the method previously described by ourselves,³ and by Haberman and Hill.⁷ The child was re-examined six hours after delivery. She was still lethargic, and still had an abnormal amount of mucus; the icterus was about the same as before, but the edema of the face and neck seemed to have increased. An icterus index at this time was 200, and the child's cells were Group B, Rh⁺ (cdE).

Since the progress seemed to be unfavorable, and since, in our experience, erythroblastotic infants showing marked edema rarely survive, it was decided to treat the child with the Rh-positive blood fraction substance which was kindly furnished by its originator. As reported elsewhere, this substance is apparently a lipid fraction from Group O, Rh-positive blood, which specifically inhibits anti-Rh agglutinins and appears to be hapten. It has proved to be antigenic in experimental animals only in the presence of a protein carrier. No local or general reaction was noted. The following morning, the edema had subsided to a marked extent, mucus was not noted, and the lungs were clear; icterus was slightly improved. The oxygen hood was removed. At that time the red blood count was 5,900,000; white count, 18,000; hemoglobin, 18 Gm.; 39 immature red cells to 100 white blood cells. No agglutinins were recovered from the child's cells. On this second day, another 50 c.c. containing 200 mg. of the Rh fraction were given intramuscularly. On the third day, all the mucus and edema were gone; the child was eating normally, artificially fed, because the mother's milk contained antibodies. The red count was 5,510,000; white count, 10,000; hemoglobin, 18 Gm.; 12 immature red cells per 100 white cells.

Further progress was relatively uneventful. The child gained normally and was discharged with the mother on the eighth day. At that time the red cell count was 5,270,000; white cell count, 13,700; hemoglobin, 18 Gm.; no immature red cells. Study of the maternal serum, six weeks after birth of the child, showed blocking antibodies in a 1:40 dilution and persistent agglutinins for cdE cells in a titer of 1:64. The child was in excellent condition, apparently normal in every respect.

In summary, we have presented a potentially severe case of erythroblastosis which was treated by the use of the nonantigenic specific Rh fraction with recovery.

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TORSION OF A PREGNANT UTERUS WITH RUPTURE*

SAMUEL L. SIEGLER, M.D., F.A.C.S., AND LOUIS M. SILVERSTEIN, M.D.
BROOKLYN, N. Y.

(From the Department of Gynecology, Unity Hospital)

SEARCH of the existing literature has revealed no report of a case of torsion of the pregnant uterus with spontaneous rupture.

Rupture of the uterus per se, due to all causes, occurred, according to Lynch,¹ 44 times out of 41,706 deliveries or an incidence of 1:1,118. Spontaneous rupture, however, occurred only in 5 cases in this series, or an incidence of 1:8,341. Cosgrove² found 32 cases in 67,000 live births with a maternal mortality of 34 per cent but makes no mention of spontaneous ruptures. Eastman,³ in discussing Lynch's paper, cited 53 ruptured uteri out of 53,000 cases or 1:1,000, out of which 17 cases, or 1:3,100, were spontaneous ruptures. At the Chicago Lying-in Hospital there were 37 cases of ruptured uteri in a total of 60,388, of which 16 cases, or 1:3,774, were spontaneous ruptures. (Adair et al.⁴) Spontaneous rupture of the uterus is a comparatively rare phenomenon.

Torsion of the pregnant uterus occurs even more rarely. Most of the standard textbooks on obstetrics make no mention of it. We are here reporting what we believe to be the first case of torsion of a pregnant uterus with spontaneous rupture.

Mrs. H. A., a 36-year-old para i, gravida ii, was admitted to the Unity Hospital on April 13, 1946 at 5:30 A.M. with a history of having been awakened from sleep by pain in the abdomen of a "sticking and cutting" character. This pain did not subside. She complained that the pain was "excruciating and unbearable," and that she did not feel her baby.

Her last menstrual period in this pregnancy was Sept. 17, 1945. She had had one normal pregnancy with spontaneous delivery eight years prior to admission. The past history was otherwise negative. She bled for one day in the 12th and in the eighteenth week of gestation. From the fourth month on, she experienced pain in the left groin and had to sit practically all the time. Throughout the antepartum period, her blood pressure ranged from 110/90 to 120/70, urinalysis negative. Two weeks prior to admission she felt contractions for two days, simulating labor pains. There was no history of a fall or other trauma. There was no history of vaginal bleeding on admission.

The patient was admitted to the hospital in profound shock. The pulse was imperceptible, the blood pressure was zero. The abdomen was tense, the uterus was hard, ligneous, and tetanically contracted. A tentative diagnosis of abruptio placentae with possible ruptured uterus was made. Plasma was started in both arms. Although conscious, she was confused, restless, and dulled in sensorium. In the fifteen minutes required to move her to the operating room, she became

*Read at a meeting of the Clinical Society of the Unity Hospital, April 23, 1947.

deeply comatose with all the signs of rapidly advancing death, i.e., dry corneas, widely dilated pupils, gasping respiration of a slow and irregular rhythm, livid and cyanotic mottling of the thighs and abdomen.

A sternal infusion was started as soon as the patient arrived in the operating room and plasma was injected by syringe. Thereafter, 2,500 c.c. of whole blood were allowed to drip rapidly through the intrasternal needle. The operation was begun without anesthesia.

At operation, a cesarean hysterectomy and a right salpingo-oophorectomy were done. Intra-abdominally there was a considerable amount of free blood. The uterus was enlarged to the size of a full-term pregnancy. There was a torsion of the uterus about its cervicouterine junction of 180 degrees and there was an inverted U-shaped rent in what was supposedly the anterior surface about 2 inches in length but which appeared to be complete. On opening the uterus through this tear, there was a considerable amount of free blood in the uterine cavity. The placenta was completely detached and there was a stillborn female about the size of a 26 to 28 weeks' gestation. The stillborn fetus was extracted and a supraecervical hysterectomy and right salpingo-oophorectomy were then performed. On examining the uterus it was found that this tear was on the posterior surface which had presented itself anteriorly.

When the operation had advanced to the point of peritoneal closure, anesthesia was started. The respirations became quicker at that time, regular in rhythm and normal in pattern. The pulse was now 110 and the systolic blood pressure 60. Relaxation was adequate but dilatation of the intestines was marked, requiring and responding to 0.2 c.c. surgical pituitrin injected intrasternally.

Pathological Report.—Uterus enlarged and ovoid in shape; measures 15 by 15 by 7 cm.; right adnexa attached. There is a horseshoe-shaped irregular tear on the posterior surface extending from midline downward, which measures 5 cm. and extends through to the uterine cavity. (Fig. 1.)

A thin-walled cystlike structure, amniotic membrane, protrudes through the internal ring. There is a small protruding nodule from the posterior wall. On section a large sac is seen occupying the endometrial cavity. No embryo or fetus is seen.

Microscopic sections show the uterus to have characteristic hypertrophy of muscle fibers. There is a large vessel suggesting a vein which is filled with a red and white thrombus. There is also a markedly elongated and wide, irregular space which in some places has a lining epithelium which suggests a vein. The lumen of the space contains a plasma and red cell clot with a high proportion of leucocytes imbedded in the clot. There is hemorrhage between the muscle fibers. No evidence of necrosis, the uterine walls show numerous trophoblastic cells invading the myometrium together with a decidual reaction.

Diagnosis.—Hypertrophy of myometrium; extensive venous dilatation and thrombus; rupture of myometrium; uteroplacental apoplexy.

Postoperatively, the patient was given supportive treatment including penicillin and repeated blood transfusions. On April 28, fifteen days after the operation, the temperature rose to 103.8° F. and she complained of severe pain in the right chest posteriorly and right shoulder. Physical examination and x-ray revealed the presence of a pulmonary infarct. Resolution was effected by bed rest, sulfadiazine, and penicillin and the patient was discharged on May 16, 1946, one month after the operation.

There was no external evidence of phlebothrombosis or thrombophlebitis on discharge from the hospital. However, twenty-one days after leaving the hospital, another pulmonary infarct occurred, from which she completely recovered.

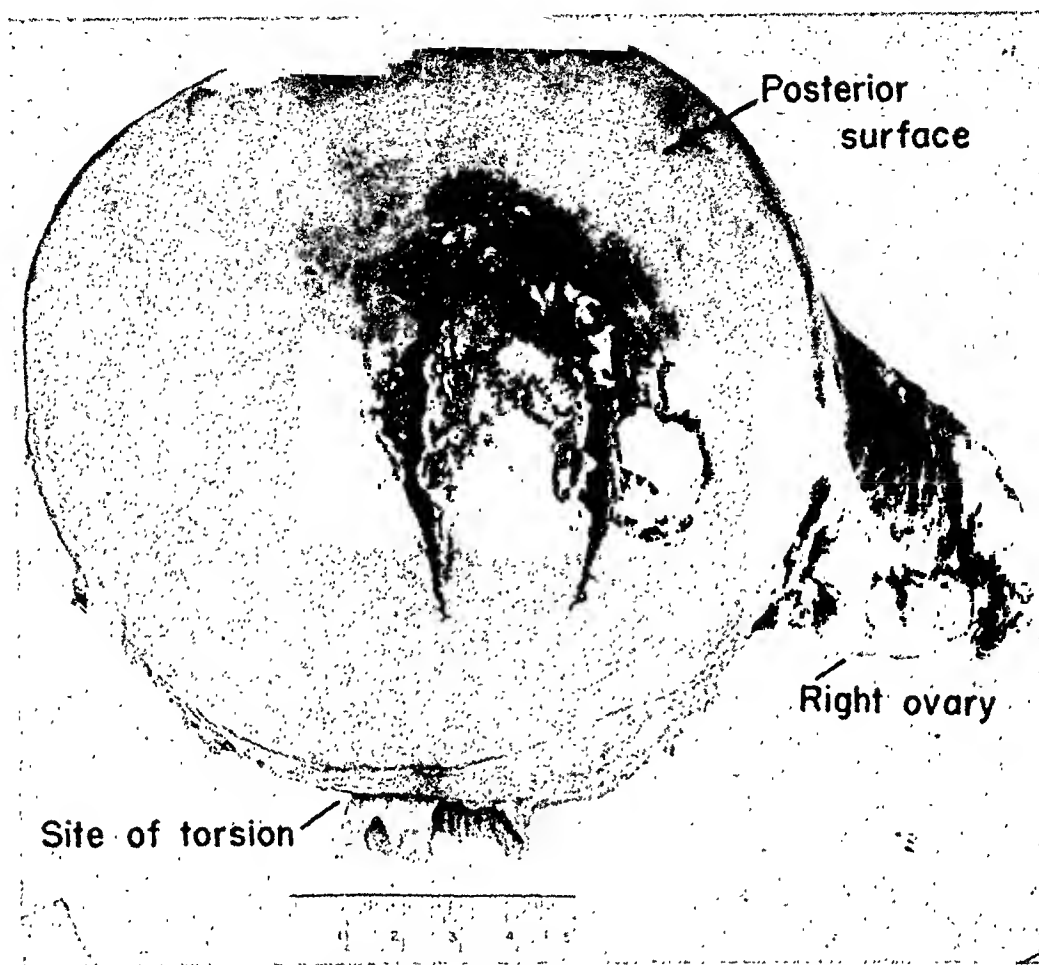


Fig. 1.—Photograph of specimen showing site of rupture on posterior surface of uterus, right tube and ovary, and where the torsion occurred in the cervicouterine junction. At operation the posterior surface of the uterus presented itself anteriorly.

Comment

Primary torsion of the pregnant uterus constitutes one of the rarest emergency conditions of gestation. Its consideration in the differential diagnosis of accidental states in pregnancy has been such that the diagnosis has scarcely, if ever, been made before treatment was instituted. The existence of torsion as a pathologic entity, although known to occur in cattle and other animals, did not appear in the literature of human beings until Virchow⁵ recorded it at a post-mortem examination in 1863.

During normal pregnancy a certain degree of torsion is present. In 80 per cent of normal cases at term, the pregnant uterus lies slightly dextroverted and twisted on itself from left to right.⁶ When the uterus rotates on its axis to a degree enough to cause arrest of circulation in the power pelvis, the torsion produces an acute abdominal syndrome and crisis.

In 1931, Robinson and Duvall⁷ summarized twenty-five previous cases of torsion in pregnancy from literature of other European authors from 1894 to

1929, and added one of their own, a case of torsion in a uterus bicornis unicollis in which the patient died unoperated upon and undiagnosed. In none of these cases was there an accompanying diagnosis of rupture of the uterus. Reis and Chaloupka⁸ reported what was practically the first case of axial torsion in which the diagnosis was made preoperatively. In their case the torsion occurred in a 25-year-old primipara, at the junction of the cervix and lower segment, and the degree of rotation was 135 degrees. The diagnosis was made when the left round ligament was palpated through a thin abdominal wall as a stretched band running diagonally to the upper right side of the abdomen. At operation no abnormalities were found in the uterus. Day⁹ reported two cases of torsion, undiagnosed, in which one was due to a large ovarian cyst and the other to fibroids in a uterus of four months' gestation. A case of 180 degree axial torsion of a gestation of eight months was reported in 1935 in which the etiologic factor was a rigid cicatricial cervix of traumatic origin.¹⁰ Recovery followed cesarean section in this case. Corr¹¹ reported a case of axial torsion of a gravid uterus in two successive pregnancies. Macleod¹² cited a case of torsion of 180 degrees in a three-month pregnancy in which a hysterectomy was performed. Bell¹³ reported a case of torsion in a pregnancy of six months' duration in which the torsion was 180 degrees. The diagnosis was not made but it was recognized as some acute abdominal condition necessitating immediate surgery. An abdominal hysterectomy was performed. Manahan and Coronado¹⁴ reported axial torsion in two cases of early pregnancy associated with myomas. Both had undergone 180 degree torsion and were subjected to hysterectomies. Smith¹⁵ reported a case of axial torsion which occurred during labor in a primipara at term. A cesarean section was immediately performed for what was thought to be an impending rupture of the uterus. In this case there was no maternal or fetal mortality.

Axial rotation of the pregnant uterus, usually clockwise, when viewed from below, may be either to the left or right although the latter is more common. The degree of rotation in most of the reported cases has been from 90 to 360 degrees. A case is reported of a pregnant myomatous uterus in which there was a torsion of 540 degrees.¹⁶ In this case the body of the uterus was necrotic.

Aside from the fact that pelvic tumors such as fibroids, ovarian masses, or adhesions can conceivably cause torsion of a pregnant uterus, the explanation for the spontaneous variety is conjectural. Here transmission of body movements, filling degree of neighboring organs, especially bladder and lower intestines, may play a role. A sudden twist or turn in bed or certain household duties may be the cause. Robinson and Duvall⁷ stated that without uterine abnormalities there can be no torsion. They believe that torsion or axial rotation in the absence of tumors or malformations is due to a developmental asymmetry of the uterine musculature.

The case cited above apparently falls into this category for there were no evidences of uterine abnormalities present. The rupture of the uterus probably occurred at the site of the greatest defect in the musculature resulting from the 180 degree axial torsion.

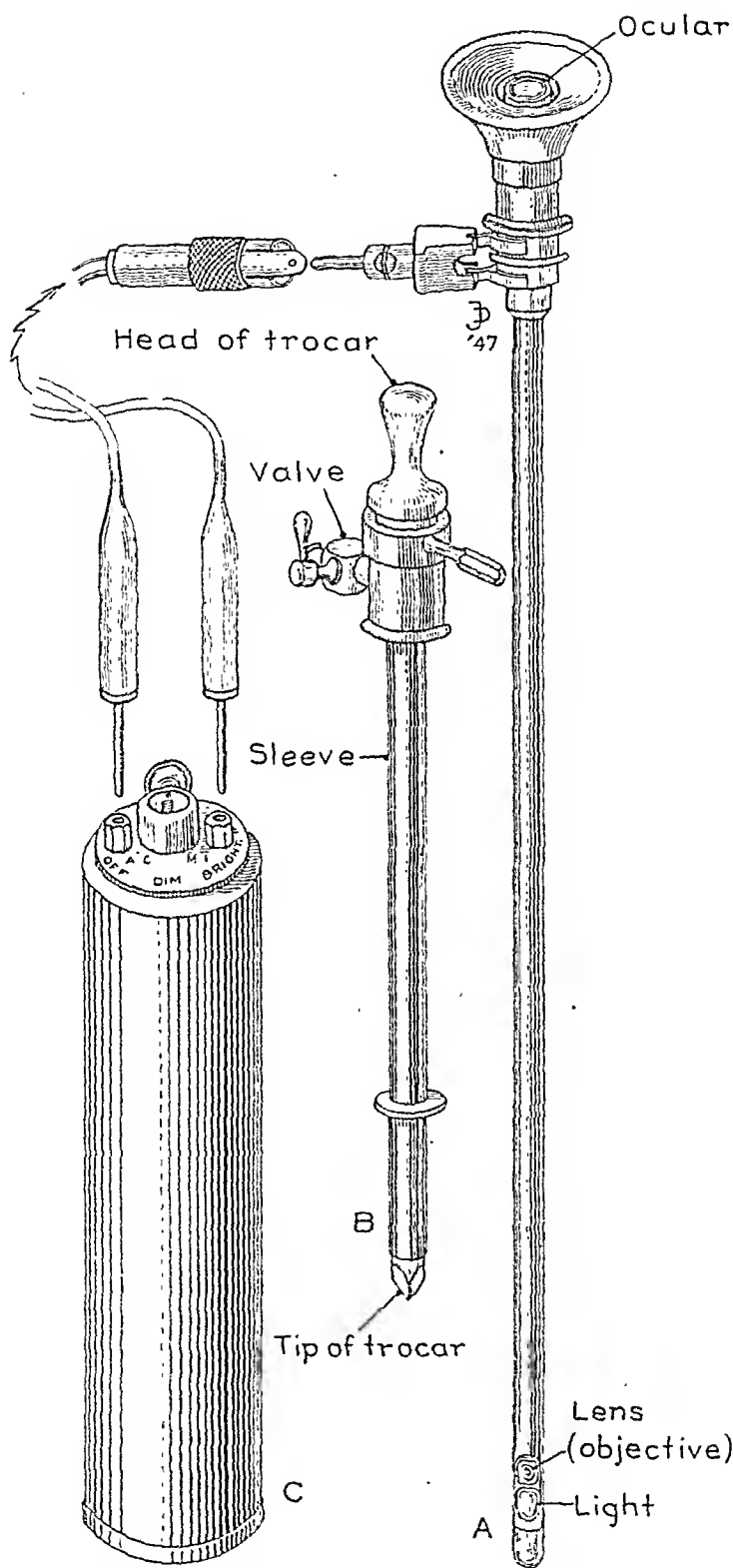


Fig. 1.—Culdoscope. Description of instrument is found in the text

OVARIAN DYSGERMINOMA*

ALPHONSE F. PAGANO, M.D., BROOKLYN, NEW YORK

(From the Department of Obstetrics and Gynecology, Norwegian Hospital)

THIS case is being presented because of the rarity of this type of specialized ovarian tumor and because of its uncertain status in regard to malignancy.

F. L., a white woman, 38 years of age, married, was admitted to the Norwegian Hospital on April 8, 1942, (No. 89190) with the following complaints: Mass in abdomen, 7 weeks, frequency of urination, 6 to 7 months, loss of 10 pounds, 1 year, and anorexia and constipation, for an indefinite time.

History.—Essentially negative except for a "nervous breakdown" five years previously and a primary amenorrhea. She had three sisters, all of whom had hypoplasia of the genital organs with sterility. These sisters were born from two different mothers, but all had the same father.

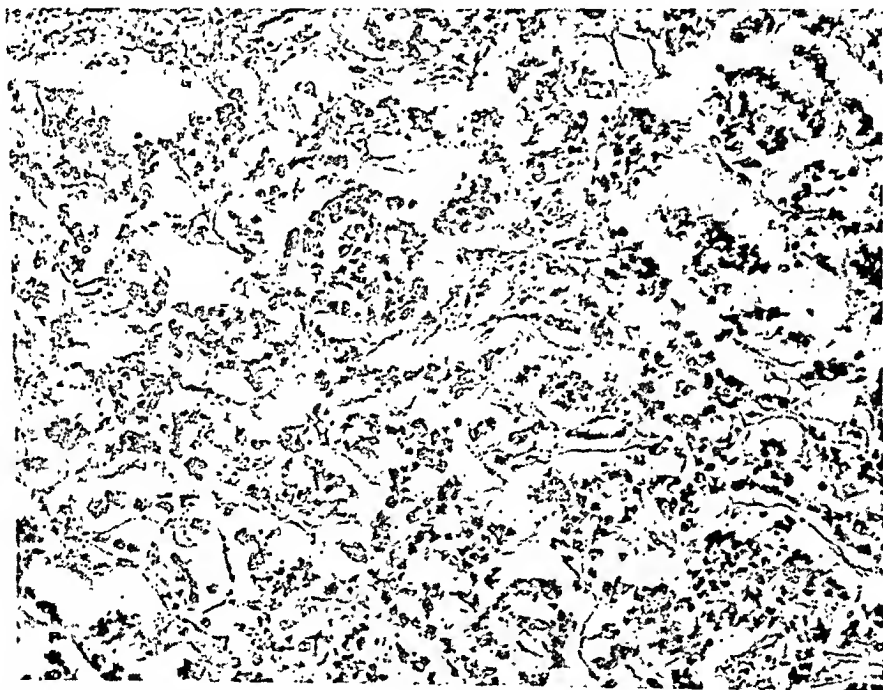


Fig. 1.—Microscopic section of tumor (X140) showing the typical architecture of the ovarian dysgerminoma, with cells arranged in alveoli, and nests with loose fibrous tissue septa infiltrated with lymphocytes.

The patient was fairly well developed and nourished, with dry skin, and in no acute distress. Breasts were poorly developed. Heart and lungs were normal. A nonpainful mass was felt, filling the lower left side of the abdomen.

Pelvic examination revealed hypoplastic external genitals and a small clitoris. The vagina was short, and a small uterus and right ovary were felt. The left ovary was found to be the seat of a large, solid tumor extending from the cul-de-sac to the level of the umbilicus. Parametrium was free.

Blood count, urinalysis, and sedimentation time were normal.

*Presented before the Brooklyn Gynecological Society, June 2, 1943.

It is to be emphasized that torsion can occur gradually or suddenly and in the latter case the symptoms are more bizarre and constitute the gravest of abdominal crises. Pain in the abdomen in torsion, uncomplicated by rupture (which will undoubtedly confuse the picture still more), usually reveals a tenderness that is not consistent throughout the entire abdomen. It is more marked within the confines of the uterus itself and usually on the side of the torsion.

Review of the literature reveals an important negative finding in cases of torsion in pregnancy, namely absence of vaginal bleeding. This we believe to be characteristic of this rare complication of pregnancy. In our case likewise there was no vaginal bleeding.

Summary

1. A case of torsion with rupture of a pregnant uterus is reported, the first to be cited in the literature.
2. The existing literature of this rare condition is reviewed and an attempt is made to present a symptom complex for torsion.
3. It is emphasized that a diagnosis of torsion in a pregnant woman is rarely made preoperatively. We should add this possibility to our list of differential diagnoses in the emergency states of pregnancy especially where there is no history of vaginal bleeding.

We wish to thank Dr. Barnett A. Greene, attending anesthesiologist of the Unity Hospital, for his anesthetic management of this case; also our thanks to Dr. W. E. Youland, associate pathologist of the Unity Hospital, for his descriptions of the specimen.

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TRUE HERMAPHRODITISM*

WILLIAM B. STROMME, M.D., F.A.C.S., MINNEAPOLIS, MINN.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

TRUE hermaphroditism, requiring for definition the presence of both ovarian and testicular tissue associated with male and female secondary sex characteristics, is an extremely rare entity. Young² was able to find but twenty authentic cases, of which only nine were proved microscopically. From time to time additional cases have since been reported. With this presentation, according to Gudernatsch,³ the thirty-ninth case has been authenticated. Case No. 38 was reported by Halpern⁴ before the New York Pathological Society in 1939, but did not receive publication.

Not long ago, I had the good fortune of studying an individual presenting both masculine and feminine characteristics. Investigation at operation and histologic study of biopsied tissue established the case as a true hermaphrodite.

J. H., aged 21 years, first came to me following her sophomore year in college, complaining of primary amenorrhea. Detailed history disclosed that at birth an enlarged penile-like clitoris was noticed. Its amputation was advised, but the parents refused. The patient's childhood was not remarkable until adolescence. Pubic hair developed at the age of 13, and during the following year her parents noted a beginning low-pitched voice and hair development on the upper lip. She was considered a "tomboy" and neighbors commented on her peculiarities. She enjoyed being with boys, playing football and baseball, and avoided companionship of girls. Family difficulties arose over these matters and her preference for wearing boys' clothes. During her late teens she became interested in girls, and on several occasions experienced penile-like erections of the clitoris, causing considerable embarrassment. In recent years she has been conscious of these abnormalities, and of failure of breast development, low pitched voice, and amenorrhea.

On admission to the hospital, examination revealed a 132-pound individual with general body contour and appearance of an adolescent male. Shoulders were broad, hips thin. She had a firm handshake, low-pitched voice, a masculine gait, and masculine carrying angle of the forearm at the elbow. Hair distribution, however, was predominantly feminine with a female type escutcheon and absence of beard, although a definite moustache was present on the upper lip. General physical findings, save for genitals, were normal.

A large penile clitoris was present, measuring 5 cm. in length. The organ was made up of two lateral corpora cavernosa penis, a well-developed prepuce, frenulum, and pseudo-glans. A central corpus cavernosum urethra was lacking, thus giving it the appearance of a hypospadiac penis with external urethral meatus at its base. Scrotal-like structures replaced the labia and separating these was a normal-appearing vaginal introitus. A vagina with hymenal opening was present, readily admitting one finger. It had a depth of 6½ cm., terminating in an infantile cervix. No testicular tissue was palpable in either scrotal sac nor could testes be found in the inguinal canal.

Routine blood studies, chemistries, and urinalysis were normal. Urine assay for androgenic 17-ketosteroid revealed an excretion of 9 mg. a day, which according to Dubriner was within normal range. Report by Papanicolaou on repeated vaginal smears

*Presented at the meeting of the Minnesota Society of Obstetrics and Gynecology, Minneapolis, Minn., May 4, 1946.

At operation, this large, solid tumor of the left ovary, with a dense nodular capsule, was removed intact without difficulty. There were no signs of any extension to the pelvic viscera.

Pathologic Report.—Tumor mass is kidney shaped, measuring 15 by 22 by 10 cm. It is covered by a smooth, dense capsule whose surface is nodular. On cut section, it is grayish-yellow in appearance and of "rubbery" consistency, with numerous areas of punctate hemorrhages.

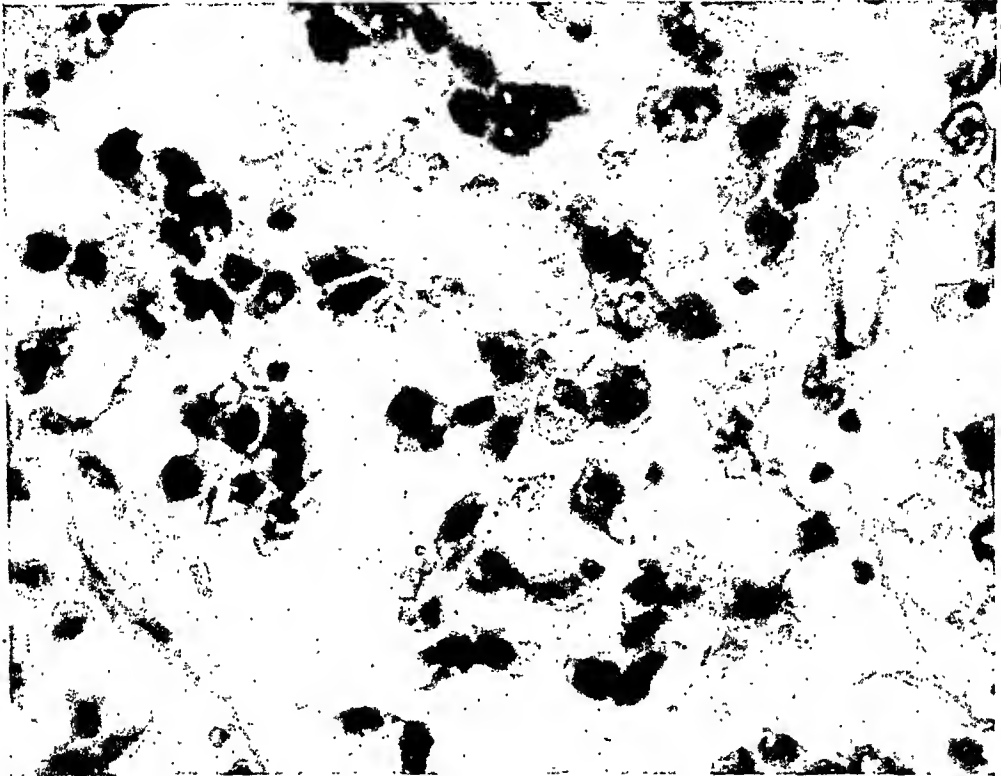


Fig. 2.—Section of tumor ($\times 650$) showing the large round or polygonal cells. The cells have large, deeply-staining nuclei, with clear, pale-staining cytoplasm, and show the alveolar arrangement and many mitotic figures. The fibrous tissue septa are infiltrated with lymphocytes.

Microscopic Section.—This shows numerous closely-packed, large round cells with light cytoplasm and large, dark-staining nuclei. The cells are arranged in nests, with thin fibrous-tissue septa infiltrated with lymphocytes. Mitotic figures are seen. The tumor is very cellular with scant fibrous tissue.

Diagnosis.—Dysgerminoma of ovary.

The patient made an uneventful recovery. Six weeks after discharge from hospital she received a course of deep x-ray therapy. She is well to date, and has gained 16 pounds.

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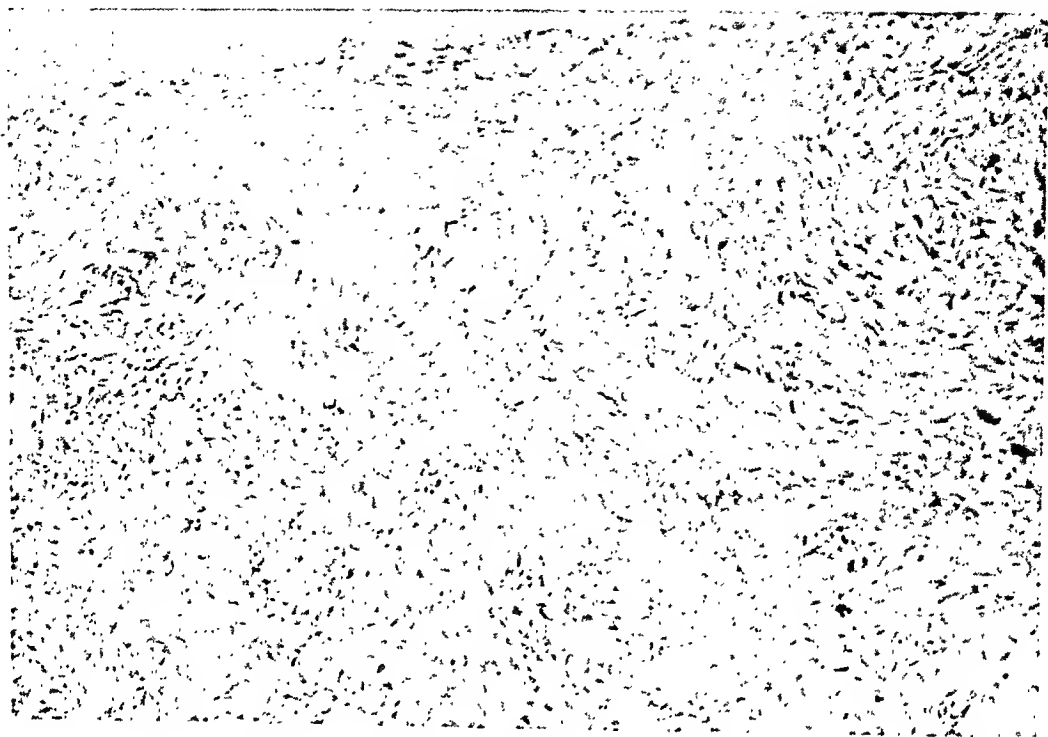


Fig. 2.—J. H. Biopsy No. 1 from left side. Tissue is fetal ovarian structure without follicles.



Figs. 3 and 4.—J. H. Biopsy from right side. Note mesonephric tubular structure and suggestion of ovarian cortical tissue.

was as follows: "Very scanty exfoliation of epithelial cells. Leucocytes relatively numerous. A few erythrocytes. The endocervical smear contains more cells, mostly cervical. The cytology is suggestive of an atrophic amenorrhea type." X-ray series of the pelvis revealed a pure anthropoid type.

At exploratory operation, the internal pelvic organs were as follows: Present in the midline was an infantile uterus consisting largely of cervix and hence intimately attached to the posterior wall of the bladder. Rudimentary round ligaments, uterovarian ligaments, and tubes were found in normal location. At the lateral terminus of the left uterovarian ligament was found a slightly thickened area, presumably ovary; biopsy was taken. A second biopsy was taken from a corresponding area on the right. Attached to the latter at its medial aspect was a pedunculated gray mass of tissue measuring 2 cm. in diameter. From it biopsy No. 3 was obtained.

Histologic study from the first biopsy revealed it to be typical ovarian cortical tissue of fetal type. No primordial follicles were found. Section of biopsy from the corresponding area on the right disclosed it to be primarily tubular structure of mesonephric origin, interpreted as rete testes. An additional section here also revealed a thin segment of undeveloped ovarian tissue. Biopsy No. 3 proved to be testicular tissue. Scattered primitive seminiferous tubules were recognizable and between these were large areas of interstitial cellular tissue. There was no evidence of neoplastic tendency.

Armed with this information, the matter was discussed at length with the patient during her convalescence. It was her wish to live as a male. Psychiatric consultant also advised that the dominant male characteristics be preserved. Hence, because of the evidence of relatively long-standing masculine tendencies based on a predominance of testicular hormonal tissue, a second operation was performed. At this time all remaining ovarian tissue was removed.

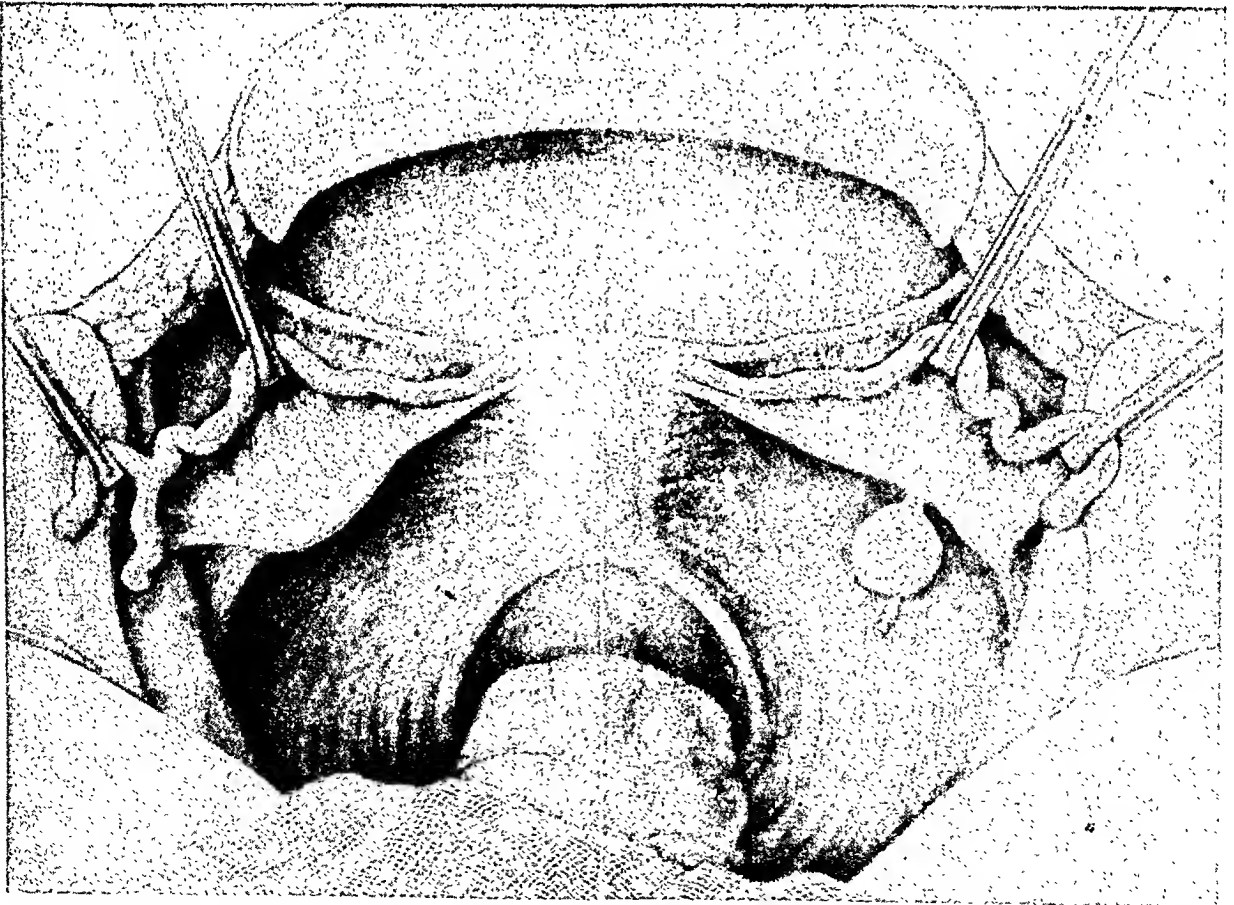


Fig. 1.—J. H. Laparotomy findings in hermaphrodite. Note infantile uterus and tubes, ovarian thickenings bilaterally, and testis on right

The patient's convalescence was again uncomplicated and *he* has since been discharged from the hospital. He acquired a man's name, haircut, and men's clothes. According to a recent letter from the patient, he adjusted well to the change, ". . . much better than I had ever dared dream." He has recently married, and writes that he is leading quite a normal life.

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731 MEDICAL ARTS BUILDING

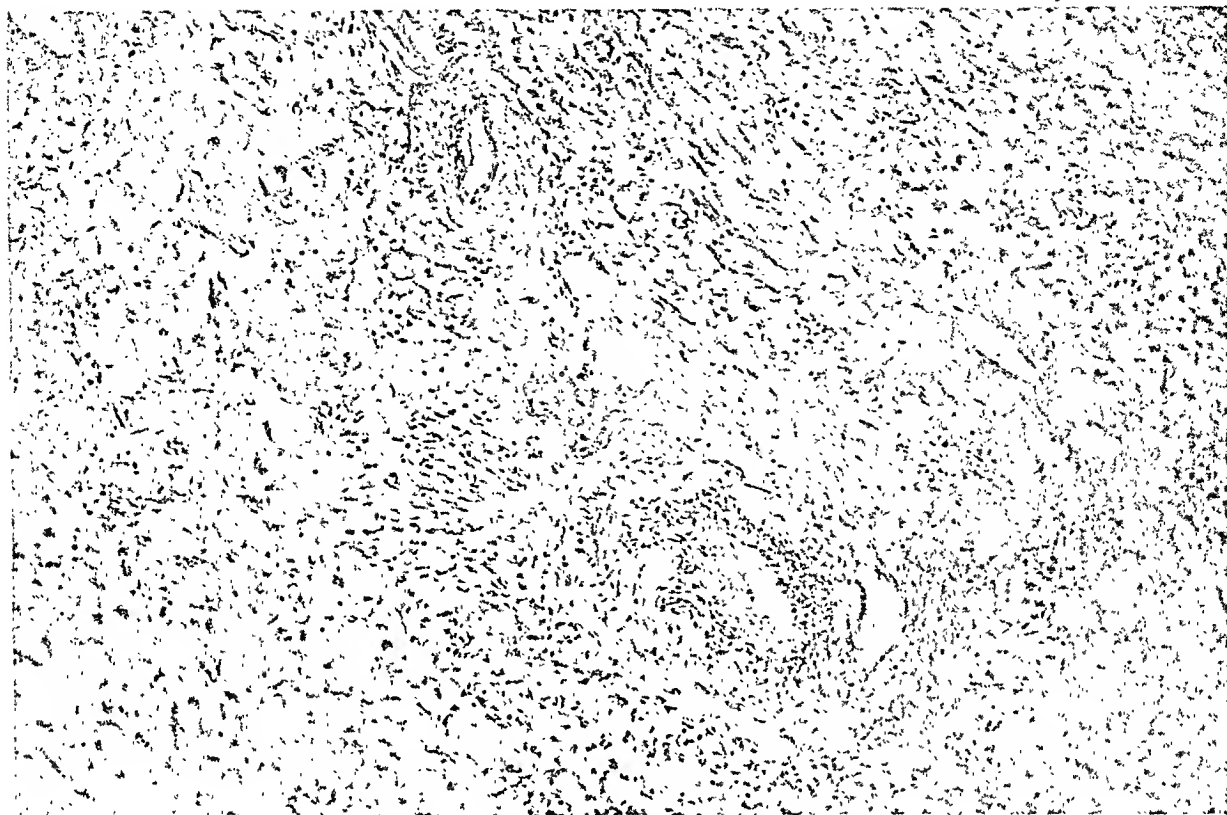


Fig. 4.—(See legend for Figs. 3 and 4.)

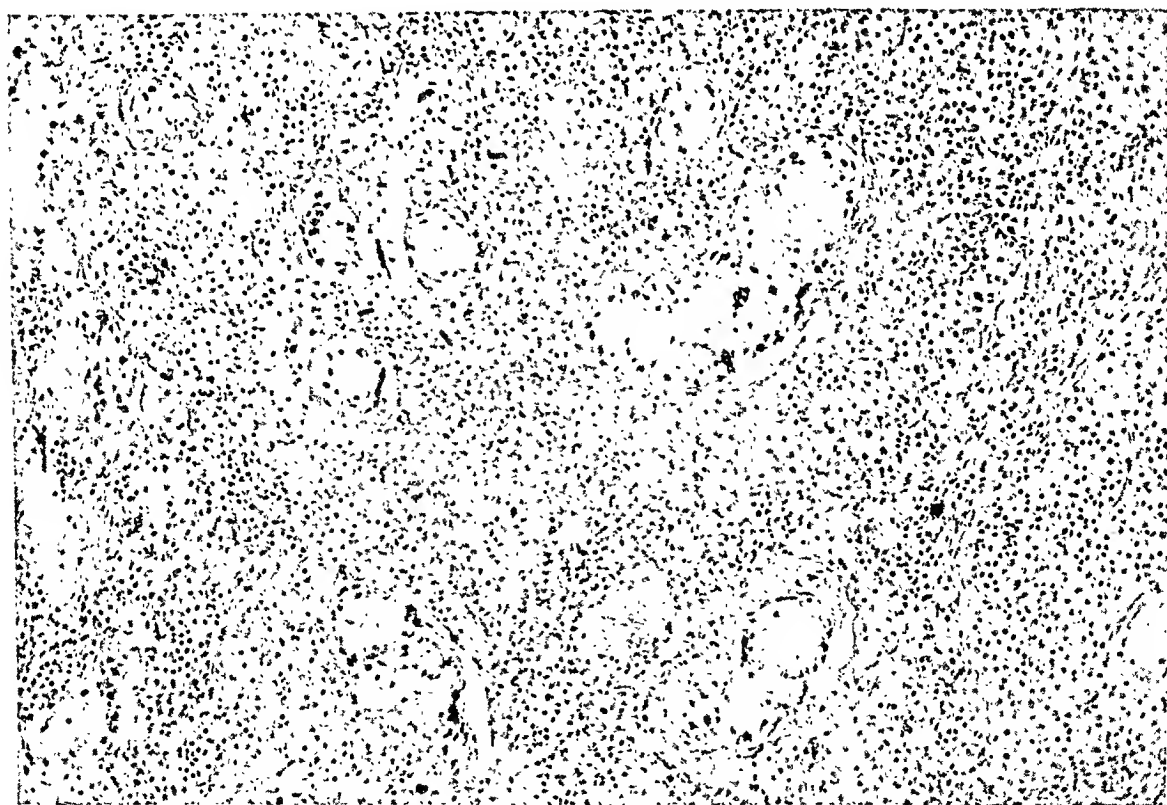


Fig. 5.—J. H. Biopsy from testis on right showing testicular tubules and interstitial tissue.

tured by a mass of clot and granular-appearing tissue measuring about 5 cm. in diameter and partially extruded through the defect in the wall of the tube. The area was markedly congested and slight hemorrhage was continuing. Before it could be removed, the mass and tube had to be freed from their adherence to the posterior surface of the broad ligament and the posterior surface of the uterus. The uninvolved portion of the left tube was of smaller than average diameter. The left ovary was larger than average and contained a prominent corpus luteum. The mesovarium was pedicle-like with a thick infundibulopelvic ligament with no discernible ovarian ligament. The ovary could be lifted freely out of the pelvis without tension on its lateral attachment. The round ligaments were of normal size and relationship to uterus and abdominal wall. The uterine cornua were equal and the uterus symmetrical although it deviated slightly to the right. The right tube was appreciably smaller than the left in the isthmic portion and continued as a barely palpable cord in the mesosalpinx which became an imperceptible fold of the broad ligament. The right ovary was not evident, either associated with the broad ligament or in the pelvis. The iliac fossa and cecal regions were searched and possible heterotopy excluded. Fecaliths were palpable in the lumen of the appendix which was then removed. Both kidneys were palpated and, with the gall bladder, were not remarkable.

The postoperative course was uneventful. The patient was ambulatory on the fourth day and discharged from the hospital on the eighth day.

The pathologist reported (1) ruptured ectopic tubal pregnancy; (2) inactive appendix. To this was added the following clinical diagnosis: congenital absence of the right ovary and hypoplasia of the right Fallopian tube.

Discussion

As in any congenital defect, a review of the embryologic development of the involved structures is illuminating.

The mesonephric body appears early in the human embryo (2.4 mm. length) and is fully developed with its duct opening into the cloaca by the end of the second month. Near the cephalic end of the mesonephros (wolffian body) an evagination of the lining of the body cavity into the genital ridge occurs. This evagination forms a tube, the müllerian duct. The converging lower portions of the müllerian and mesonephric ducts are embedded within a median band, the genital cord. The development of the ovaries begins about the time the müllerian ducts are forming. The ovaries are evident first as linear thickenings of the mesothelium and underlying mesodermal stroma on the median surfaces of the mesonephric bodies. The latter are enclosed and attached to the posterior body wall by mesenteries which continue as folds to the diaphragm and then inferiorly to the inguinal region. The early ovary is also provided with a mesentery that is continuous above and below with the folds of the mesonephros. The more important and prominent of the two is the lower plica in which lies a fibromuscular strand (the ovarian ligament) which below is attached to the müllerian duct. A second band of muscular tissue appears within the lower part of the inguino-mesonephric fold and has as its upper attachment also the müllerian duct at a point about where it received the insertion of the ovarian ligament. The lower end of this band blends with the subperitoneal tissue in the vicinity of the future abdominal inguinal ring and later becomes the round ligament of the uterus. The müllerian ducts below the attachments of the ovarian ligaments fuse to form the uterus and vagina. Above the attachments they become the uterine tubes. The broad ligaments are formed by the enlargement of the primary peritoneal fold containing the müllerian and mesonephric ducts.⁶

Examination of the adult specimen does not tell us where in this orderly and integrated process interruption occurred, except that it was probably early. We may summarize then that in this case in the inguinomesonephric plicae the lower fibromuscular bands were normal, for both round ligaments were fully developed. The upper paired bands or ovarian ligaments originating on the ovaries and inserting on the müllerian ducts were of less than normal development on the left and indiscernible on the right, as was any significant development of the right ovary. Above the attachment of the round ligament on the right, the müllerian

CONGENITAL ABSENCE OF ONE OVARY ASSOCIATED WITH CONTRALATERAL TUBAL PREGNANCY

JOSEPH A. KURCZ, M.D., AND MAHLON S. SHARP, M.D., LANSING, MICH.

(From the Department of Gynecology of Woman's Hospital)

CONGENITAL absence of an ovary is an unusual finding, although White¹ in 1935 was able to collect seventeen cases in the world's literature, and about twenty-three cases have since been reported. An appreciable number of these cases have been in women who have borne one or more apparently normal children.^{2, 3} One instance of tubal pregnancy associated with a deformed tube and aberrant ovary⁴ was found, and another single instance of tubal pregnancy in a patient with only one tube and one ovary⁵ has been described. Encountering these last-mentioned conditions which have apparently only once previously been reported makes the following case worth reviewing.

Case Report

Mrs. L. D., a 30-year-old white housewife, had been married about seven months when she was admitted to Woman's Hospital complaining of pain in lower abdomen and a feeling of weakness.

The present illness had begun fifteen days previously when, about two weeks after an expected menstrual period, she first noticed slight vaginal bleeding. She continued to feel well and performed her usual activities. After eight days of continued spotting, bleeding stopped for two days and then began more vigorously as a moderate bright red flow accompanied by irregular cramping pain in the lower abdomen. At bedtime the pain became more severe and she fainted. When she recovered, the pain seemed to be gone but returned two days later and this time was so severe that she remained in bed. She noticed small clots and the vaginal bleeding was slightly heavier than the usual menstrual flow. The abdominal pain became more severe and she called a doctor who sent her to the hospital by ambulance. Weakness was most marked at this time. The appetite had been poor for three days, although there had been no nausea, vomiting, or change in daily bowel habit. She had noticed no breast changes.

The past history revealed no operations or serious illnesses. The family history was not remarkable. She had been treated for cystitis in July, 1946, and cystoscopy was performed later.

The physical examination on admission revealed normal nutrition and feminine development. Skin and mucous membranes disclosed moderate pallor. The lips and tongue were dry. The heart, lungs, and breasts were not remarkable. The abdomen was moderately tender in the left lower quadrant. Vaginal examination was significant in that the posteriorly directed, nulliparous cervix was exquisitely tender on slight movement. The uterus was forward and nongravid in size and consistency. It was slightly fixed to an ill-defined tender mass in the left adnexal region.

The laboratory reported the urine to be normal except for numerous yeast cells. Hemoglobin was 12.6 Gm. per 100 c.c. of blood; R.B.C., 3,750,000; W.B.C., 9,000 per cubic millimeter of blood, with P.M.N., 86 per cent (F., 76 per cent; N.F., 10 per cent); basophiles, 1 per cent; and lymphocytes, 13 per cent. The department of radiology reported upon a retrograde pyelogram (Nov. 4, 1946) as follows: "Chronic pyelitis, bilateral, and beginning hydronephrosis on the right. No stones were visualized."

The patient was operated upon the evening of admission with the diagnosis of ruptured left tubal pregnancy. The abdomen was opened through a paramedian incision and about 200 c.c. of partially clotted blood was found in the lower peritoneal cavity. The uterus was small and in anterior position. The outer third of the left tube was distended and rup-

make the abdominal contents visible through the ocular. Just distal to the objective lens is a small electric bulb which is illuminated by means of a dry cell battery. The one pictured in Fig. 1 is the one supplied by the manufacturers, but we have made a larger one which gives better illumination.

The Procedure.—The patient is placed in the knee-chest posture. Various devices have been designed to hold patients in the knee-chest position, but for the most part they appear to be of more trouble than value. If the culdoscopic examination is to be made with the patient awake, she can maintain the position unsupported for a time sufficient to permit completion of the examination. If the examination is to be made under general anesthesia, she can be held in position quite satisfactorily by an intern or nurse standing on either side of her with the adjacent arm encircling the patient's thigh. If the patient is in proper position she need only be kept in balance which requires very little effort.

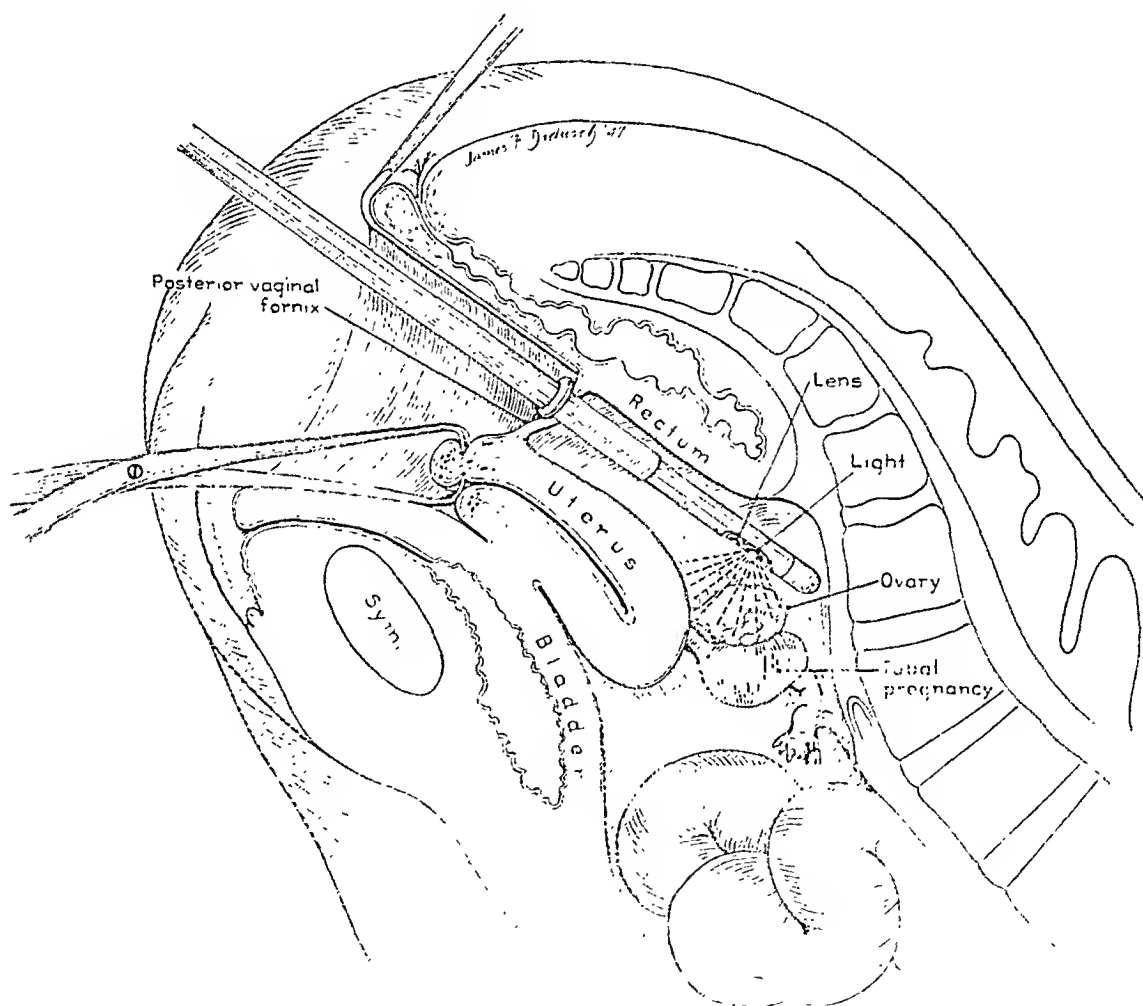


Fig. 2.—Sagittal view showing the patient in the knee-chest posture and culdoscope in place. Note how the intestines fall away from the pelvic viscera.

The vagina is cleaned up as for a vaginal plastic operation. If the patient is unanesthetized, care must be taken to use a nonirritating antiseptic solution.

We have done the endoscopic examination on many patients under local anesthesia by simply injecting several c.c. of 0.5 per cent nupercaine solution in the posterior vaginal fornix at the site of puncture of the trochar. When gen-

duct was similarly and cephalad progressively involved in agenesis. This defect also, it is felt, was to some extent bilateral for at least some degree of hypoplasia of the left tube is believed to have been present.

In the case described the defect was less extensive than that in many previously reported, although in the five patients seen at Mayo Clinic³ four of them had borne normal children. Lajos⁷ reports Kossmann's analysis of twenty-two cases which revealed grossly normal uteri in six, and Reifferscheid, who with others, has observed that anomalies of the kidney are commonly associated with this defect and that the kidney and ureter of the same side may be absent. The kidney and ureter in this case were studied and showed no congenital defect. The ovary is more frequently absent on the right. Only five cases were encountered wherein this degree of agenesis was bilateral.

Curtis,⁸ in discussing the etiology of tubal pregnancy, says that in the past, non-inflammatory mechanical factors have been given too little emphasis and feels that congenital malformations may frequently be responsible for ectopic nidation. TeLinde⁹ and others mention the not infrequent but difficult demonstrable diverticuli as occasional cause of gestation within the uterine tube. Other authors describe accessory ostia and lumina, excessive folding of the tubal mucosa, and the persistent fetal type tube which is long and much convoluted as possibly significant predisposing congenital conditions. It is also reasonable that simple hypoplasia with perhaps a much narrowed lumen and impaired peristalsis could be an explanation in this case.

Summary

1. A rare anomaly of unilateral absence of the ovary and partial agenesis of the corresponding tube has been described.
2. Ectopic pregnancy of the opposite tube occurred associated with this abnormality; hypoplasia of the tube is considered the probable etiology.

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PREGNANCY FOLLOWING AN INTERILIO-ABDOMINAL AMPUTATION

(Sacroiliac Disarticulation or Hemipelvectomy)

HOWARD L. WILCOX, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

ONLY one other case of pregnancy following amputation through the sacroiliac joint has been noted in the literature. That case is reported by Judin,¹ a Russian surgeon. He did a radical amputation because his patient had a chondrosarcoma involving the upper third of the right thigh and the right inguinal region. Approximately five months after the operation she became pregnant. At term, the patient was admitted prior to the onset of labor so that a cesarean section could be done if necessary. However, she spontaneously delivered a 4,200 gram infant after one-half hour of labor. (That was her ninth baby.) When the patient was heard from one year after delivery, she was in good condition and had just stopped nursing her baby.

According to Paek and Ehrlich,² only one hundred thirty-two cases of amputation through the sacroiliac joint have been reported in the literature in the past fifty years. Six more cases were reported by Paek and Ehrlich. Thus, there is now a total of one hundred thirty-eight such cases. The case now being reported was presented, prior to pregnancy, in the hemipelvectomy series by Dr. Paek² (Case 4).

Case Report

The patient was a 24-year-old white primigravida. She presented herself in our obstetric clinic with a letter from the Memorial Hospital where the hemipelvectomy had been done. This revealed that on June 15, 1945, a left sacroiliac disarticulation had been carried out for a malignant neurofibroma of the von Recklinghausen type. It had involved the sciatic nerve and its branches and extended into the muscles of the thigh and buttock. The obturator foramen had been perforated and the pelvic parietes likewise were involved. One year after her operation the patient married. Her last menstrual period was on Aug. 2, 1946. Her expected date of confinement was computed to be May 9, 1947. When the patient was first seen in the obstetric clinic, the general physical examination was essentially unremarkable, except for the sacroiliac amputation. Her serology was negative and she was found to be Rh negative. Repeated transfusions had been given to the patient during and following the operation. On closer examination of the operative site, some tenderness was noted and the labia on the left were edematous. Rectal examination revealed a mass extrinsic to the bowel which caused a partial occlusion of the rectum. In January of 1947 it was apparent that this mass was enlarging. Therefore, the patient had an aspiration biopsy done at the Memorial Hospital which revealed a neurosarcoma, considered to be recurrent in origin. After careful evaluation, it was felt that the prognosis of the patient was hopeless, and therefore the pregnancy should be allowed to continue, with the hope of getting a live baby. Pain throughout the surgical stump, lower abdomen, and back became quite constant and annoying. Sedatives and analgesics were administered, and it was planned to give palliative x-ray therapy after delivery of the infant.

On March 11, 1947, the patient was admitted to the obstetric service with the signs of early premature labor. The pain in the stump had become excruciating in nature. There was some bowel distention associated with nausea and vomiting. This was controlled with supportive measures. The uterine contractions were stopped with the use of morphine. Two days later, vaginal examination revealed the presence of marked edema of the left

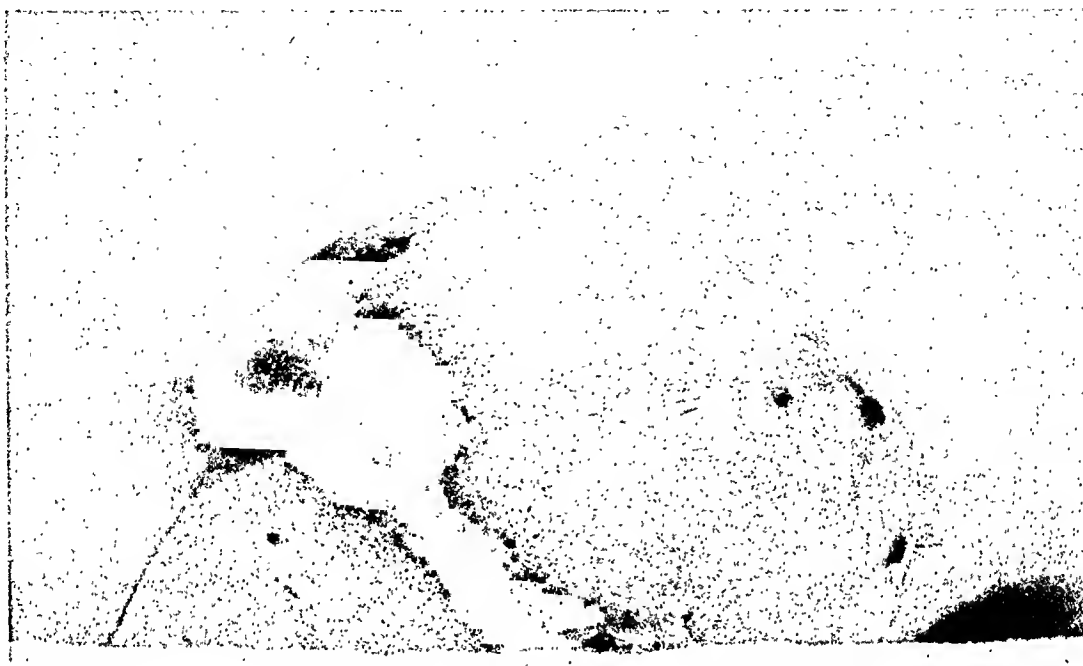


Fig. 1.—Lateral view of patient revealing surgical absence of the left leg. The left side of the pelvis (the bony wall of which was removed) is now replaced by tumor mass. Note edema and discoloration of the overlying skin and the marked edema of the left labia.

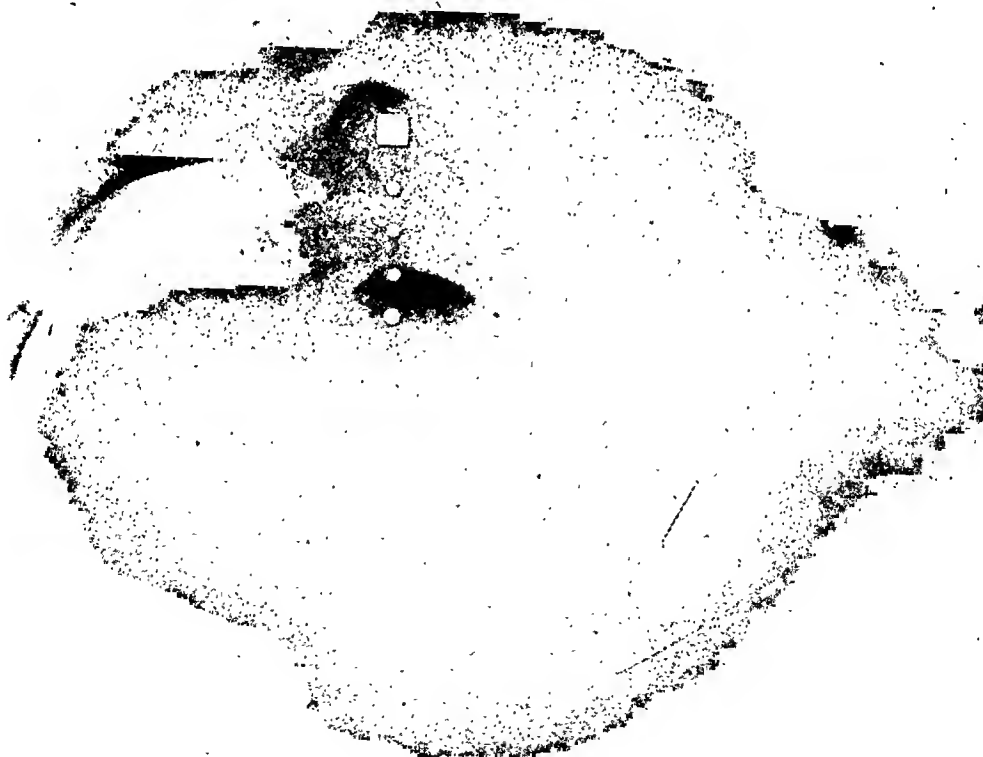


Fig. 2.—X-ray of the pelvis reveals absence of the bony structures on the left. Note soft tissue mass on left side extending over to the midline of the pelvis.

labia. There was some relaxation of the vaginal canal. The obstetric conjugate was ample. On the left side, a hard spherical mass extended to the midline. X-rays of this area revealed a large, soft tissue mass that extended to the sacrum with evidence of bony erosion.

The clinical course was rapidly downhill. Anorexia, nausea, and vomiting developed. Intravenous fluids, transfusions, and sedatives were administered. A low-grade temperature developed. It was apparent that the patient would not live to go to term. The fetus was estimated to be about 2,200 to 2,300 grams. Since the patient was Rh negative, her blood was tested for antibodies; she was found to have a weak blocking antibody titer of 1:2 and 1:4. On March 20, a classical cesarean section was carried out in an attempt to get a living baby prior to the certain exitus of the patient. A 2,500 gram male infant was born and appeared to be in good condition. A specimen of cord blood revealed the infant to be Rh negative. Unfortunately, the baby did not do well during the next few days. Marked edema and jaundice developed and, fifty-eight hours after delivery, the infant expired. Autopsy examination revealed the baby to have atelectasis with marked edema and jaundice.

The mother was given supportive measures following the cesarean section. This consisted of multiple transfusions of whole blood, infusions of plasma, glucose, and vitamins. Progressive weakness, edema, pleural effusion and pneumonia developed. On April 11, 1947, the patient expired.

The significant autopsy findings revealed the presence of multiple neurogenic fibromata with neurogenic sarcoma of the left buttock. The left femoral and sciatic nerves, together with most other nerves distal to the intervertebral foramina in this region, were irregularly and several times enlarged by firm gray-white tumor tissue. Densely adherent to these nerves, extending laterally into the left buttock and medially invading the sacrum was a 20 by 15 by 15 cm. firm gray-white mass with small central areas of hemorrhage and necrosis. Many nerves throughout the body, including both vagi, phrenics, and the right femoral and sciatic nerves, were greatly (up to about eight times normal size), but variably, often locally, enlarged. Metastatic sarcoma was noted by the invasion medially into the sacrum. There was also a single (1 by 0.5 cm.), gray-yellow, firm metastatic tumor nodule beneath the pleura of the upper lobe of the left lung. Together the lungs weighed 1,300 grams and were markedly hyperemic and edematous with large firm areas of consolidation in all lobes. There was a firm red infarct, measuring 4 cm. across, in the lower lobe of the left lung, with a medium-sized artery occluded by a firm grayish red thrombus. *Staphylococcus aureus* hemolyticus and a pneumococcus, unclassified, were grown from the lungs post mortem.

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Correspondence

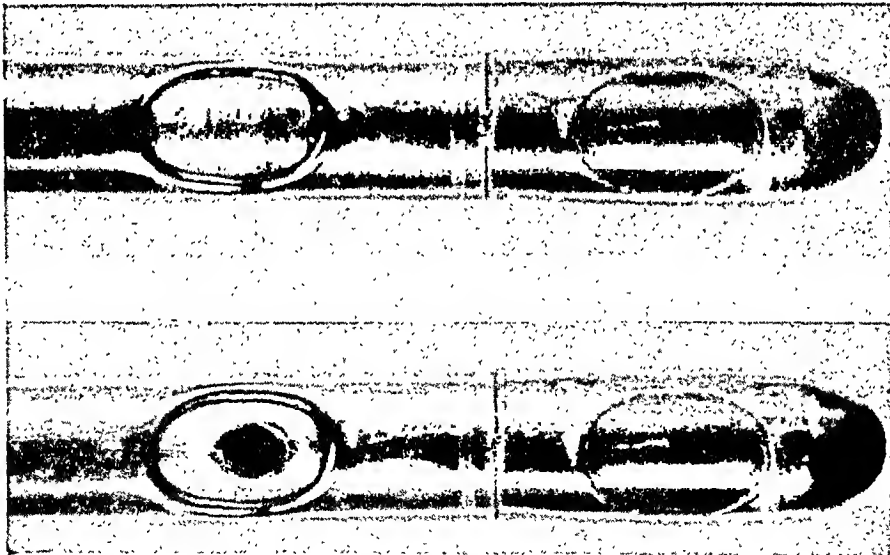
Culdoscopy

To the Editor:

I have read with great interest the article on culdoscopy published by R. W. TeLinde and F. Rutledge in the January, 1948, issue of the JOURNAL. As far back as 1936, I introduced the first instrument designed for this type of examination and named it colpolaparoscope. Having gained considerable experience with colpolaparoscopy (method of entering the abdominal cavity through the fornix vaginae), I wish to state that I am in complete agreement with the aforementioned authors, that colpolaparoscopy (c. 1.) is a useful adjunct to the diagnostic armamentarium in gynecology. However, it should be stressed that, in addition to colpolaparocentesis as a therapeutic measure in conditions associated with ascites, I used the operative colpolaparoscope for minor surgical procedures such as the dissection of adnexial adhesions, fimbriolysis, and the securing of biopsies.

My instrument was manufactured in Vienna, in 1936, by the Leiter Company. It is equipped with an elaborate optical system, and a device which prevents the lenses from becoming soiled within the abdominal cavity. The lenses are covered during the introduction of the instrument. (Fig. 1A.) With the instrument in situ, the rod equipped with the optical system is rotated within its sheath clockwise 180 degrees. Thus the lenses are set free. (Fig. 1B.) Two close-up pictures of the proximal part of the instrument, demonstrating this mechanism, are attached; also a picture of all the component parts of the instrument (Fig. 2).

A.



B.

Fig. 1.

Only when the examiner is certain that the cul-de-sac of Douglas is free should the brusque penetration in knee-chest position be attempted. In all other cases, the anatomic approach to the pelvic cavity through a 1 cm. wide incision in the posterior fornix, with exposure of the rectovaginal space and the peritoneal reflection, is preferable. This approach was advocated by me in presentations before the Viennese Medical Society, 1937, and the New York Academy of Medicine, 1947, and described in *Wien. klin. Wchnschr.* 59: 50, 1947. The delay in publication was due to the war and postwar conditions. By the ana-

tomic approach to the cavity of Douglas, its contents, such as blood or exudate, will not escape the attention of the examiner, and injuries to a viscus and extra- or retroperitoneal emphysema will be avoided. Failures to penetrate into the abdomen, as encountered by Rock in one out of every six of his cases, may thereby be markedly reduced.

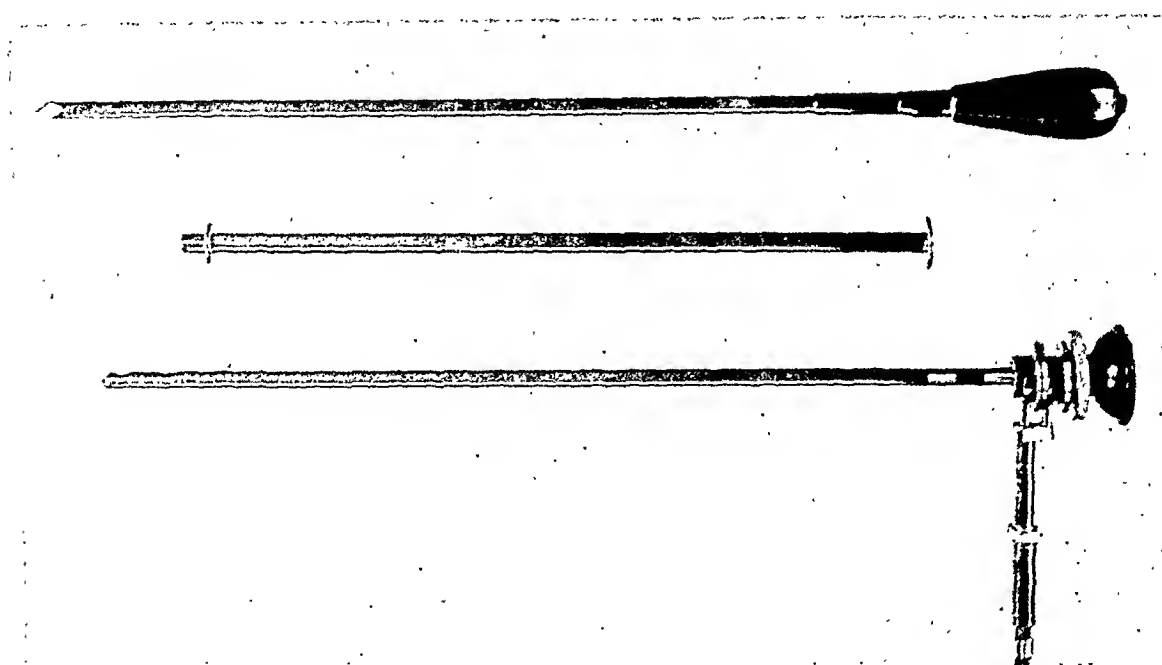


Fig. 2.

We have used two methods of introduction of the instrument: (1) in Trendelenburg position with the operating table tilted at an angle of 45° , with air insufflation and an intrauterine probe, which keeps the uterus in position; (2) in knee-chest position. In either case the instrument should be inserted with its proximal end directed toward the center of an imaginary line, which connects the promontory with the umbilicus.

There are two definite and strong indications for performing a colpolaparoscopy: (1) all instances suggestive of ectopic pregnancy (peritubal hematoma, hematomole, early tubal abortion, etc.) where otherwise, a diagnosis cannot be made with certainty; (2) cases of ovarian or tubal carcinoma or cancers of adjacent pelvic organs. In these two categories, a definite diagnosis can be established and a lifesaving operation performed without delay. Episodes, such as torsion of the uterus or adnexa or bleeding from a ruptured corpus luteum, can be diagnosed and treated surgically. Furthermore, it is helpful in avoiding unnecessary laparotomies in cases of subacute and chronic inflammations, in small fibroids, which by virtue of their localization are often mistaken for ovarian tumors, in endometriosis, etc. There is also a definite place for examination in cases of sterility due to ovarian conditions, such as infantilism or adnexial adhesions, both of which can easily be visualized, and the latter sometimes successfully treated with the operative colpolaparoscope. However, in order to guard the new method against becoming discredited, it should never be performed indiscriminately. The method is definitely contraindicated in febrile conditions or infectious diseases of the genital tract and its adjacent organs.

The valuable contributions by TeLinde and Rock will hasten the introduction of the procedure into gynecology. May I add that the foregoing communication is not intended to detract from the valuable work of Dr. Decker.

EMANUEL KLAFTEN, M.D.

333 CENTRAL PARK, WEST
NEW YORK
Feb. 14, 1948

Cesarean Section Scar

To the Editor:

I have been much interested in the study of cases of rupture of the abdominal scar of previous cesarean sections, from the Boston Lying-in Hospital, as presented by Daniel H. Hindman, in the February number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

While I was a member of the Staff of the Maternity Hospital of Cleveland, we saw a patient who had had a previous section because of disproportion. We brought this patient into the ward for the last few weeks of her next pregnancy. At the first intimation of labor, a repeat section was started. On opening the abdomen, I found the line of the former classic section in the uterine wall was represented by a soft red stripe of granulation-like tissue. At one point, this had already separated for a distance of some two centimeters. Through this opening, the unruptured fetal membranes herniated. The gloved finger introduced here easily separated the entire length of the old incision, and the baby was delivered without the use of any incision in the uterine wall. Microscopic examination of the red tissue forming the old scar showed it to be endometriosis extending from the uterine cavity. In weighing the pros and cons for a repeat section, this possible weakening of the old scar should be borne in mind.

Another factor that should be studied, when the question of section or vaginal delivery must be decided in such cases, is the position of the placenta. I was impressed—I think there were four cases—with the apparent fact that a placenta on the front wall of the uterus makes the old scar of a classic section more vulnerable. Possibly this is due to invasion of trophoblast and increased vascularity under the placenta. By noting the direction of the round ligaments, or by x-ray, it is usually possible to tell whether the placenta is on the anterior or the posterior uterine wall. That position is well worth evaluating in making a decision about the need for repeat section.

JOSEPH T. SMITH, M.D.

30 BENNET STREET
BOSTON, MASS.
MARCH 24, 1948.

Erratum

In the article by Peter J. Talso and William J. Dieckmann, entitled "Anemias of Pregnancy," in the March issue of the *JOURNAL*, the accompanying two illustrations were printed with the explanatory material deleted. They are reproduced here with their complete legends.

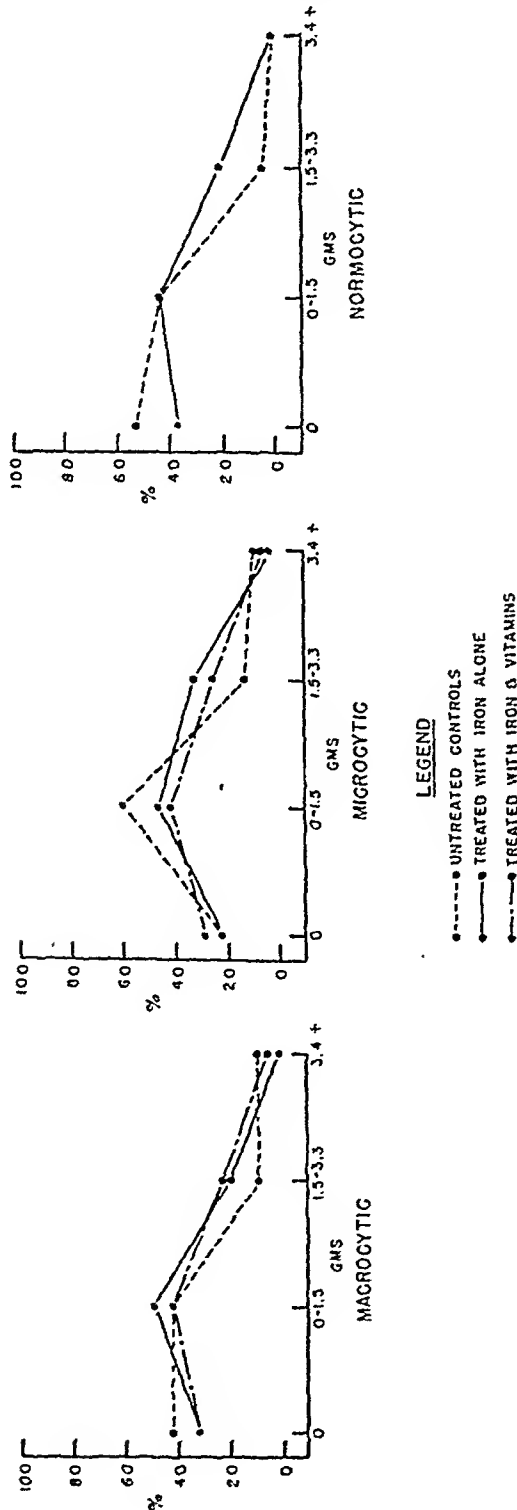


FIG. 1. PERCENTILE DISTRIBUTION OF GAIN IN HEMOGLOBIN DURING 21 DAY OBSERVATION PERIOD

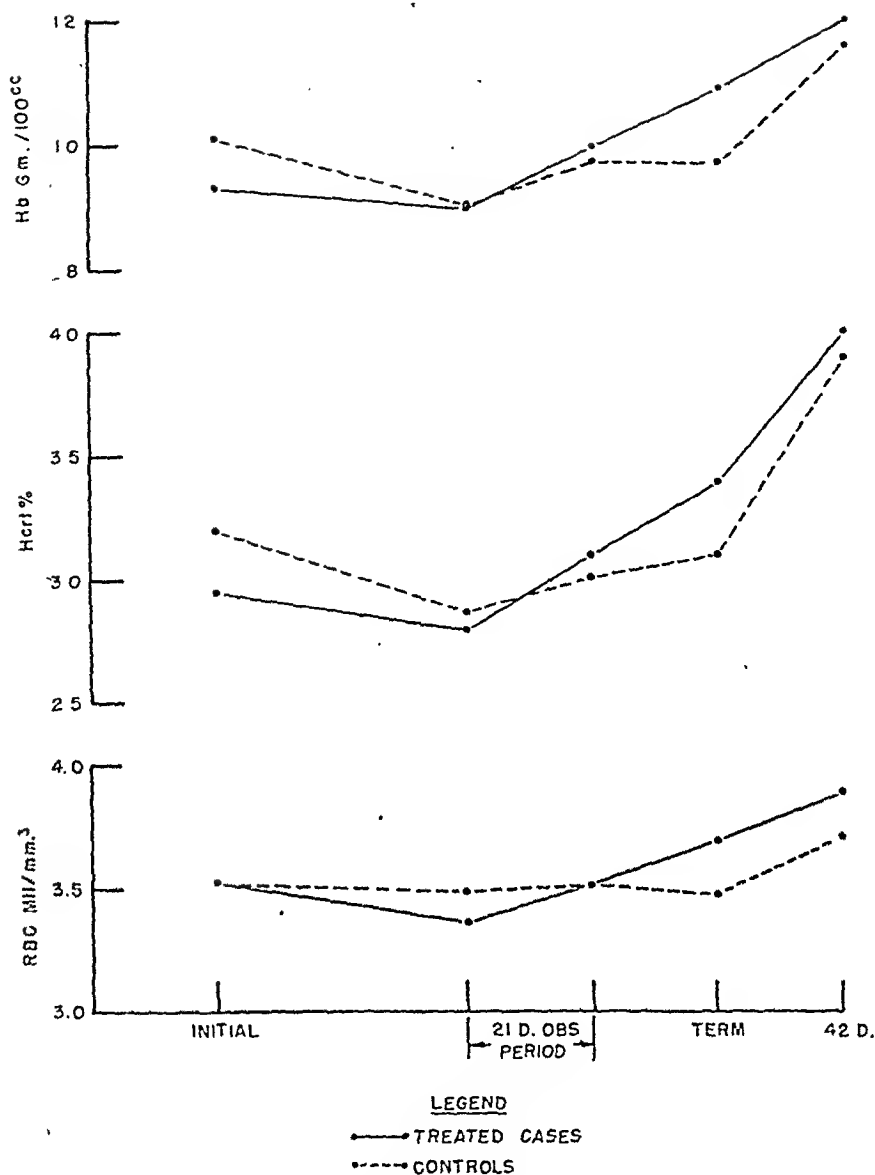


FIG. 2. MEAN VALUES FOR HEMOGLOBIN, HEMATOCRIT AND RED BLOOD CELL COUNT.

Erratum

In the article by Wesley Bourne, entitled "Wise Indifference of the Wise in Anesthesia," in the April issue of the JOURNAL, on page 714, in the nineteenth line, the word "either" should read "ether"; on page 715, in the thirty-seventh line, the word "pyruvid" should be "pyruvic."

Department of Reviews and Abstracts

Selected Abstracts

Menopause

Ingiulla, W.: Endocrine Factors and Abnormal Uterine Bleeding During Climacteric, Riv. Ital. di Ginec. 28: 77, 1945.

Profuse uterine bleeding during the climacteric, without anatomic change in the womb, was observed in nineteen cases by Ingiulla in the Department of Gynecology of the Medical School in Florence. None of the patients in this group showed the more common climacteric signs of hyperactivity of the corticoadrenal system, such as flushes, hypertension, adiposity, or hirsutism. Signs and symptoms reminiscent of hyperthyroidism, however, were frequently present, such as tremor, instability, and insomnia.

The research work is based on painstaking observation of clinical signs and symptoms, and findings are interpreted according to the teaching of De Giovanni and Marañón.

Climacteric patients with essential bleeding observed by Ingiulla showed constitutional characteristics usually seen in the so-called underdeveloped or juvenile type.

According to Ingiulla, juvenile constitution with latent hyperthyroidism seems therefore to be the foremost underlying factor in essential profuse bleeding during the climacteric.

GEMMA BARZILAI.

Cazzola, D., and Mosconi, G.: Saccharomyces in the Vaginal Cycle, Riv. Ital. di Ginec. 29: 152, 1946.

Cazzola and Mosconi of the Obstetrical and Botanical Department of the Medical School of Pavia made proportional countings of saccharomyces colonies, cultivated from the vagina of six healthy women. Saccharomyces appeared to be a normal finding in the vaginal content of healthy, normally menstruating women.

The proportional counting of the colonies also showed a definite pattern of rising and falling, according to and coinciding with the different periods of the monthly cycle. Highest values were found around the twentieth day of the cycle, with progressive rising from the tenth to the twentieth day of the cycle (intermenstrum). Lowest values were found during actual menstrual flowing with progressive fall starting after the twentieth day of the cycle.

Saccharomyces are found again in cultures made five to six days after cessation of the menstrual flow, and they rise progressively until the twentieth day.

During the monthly pregnancy, colonies of saccharomyces are extremely numerous.

During the monthly cycle, highest value of saccharomyces coincide with the period in which the vaginal epithelium is richest in glycogen and the chemical reaction is more definitely acid (pH about 4.5).

GEMMA BARZILAI.

eral anesthetic is used, we have chosen intravenous pentothal sodium in 2½ per cent solution. It is usually given through a vein in the dorsum of the hand or wrist after the patient has assumed the knee-chest posture. We have chosen general anesthesia for those patients who appear to be rather nervous, and for those upon whom we have felt that immediate laparotomy was likely. All of our patients have been hospitalized for at least twenty-four hours.

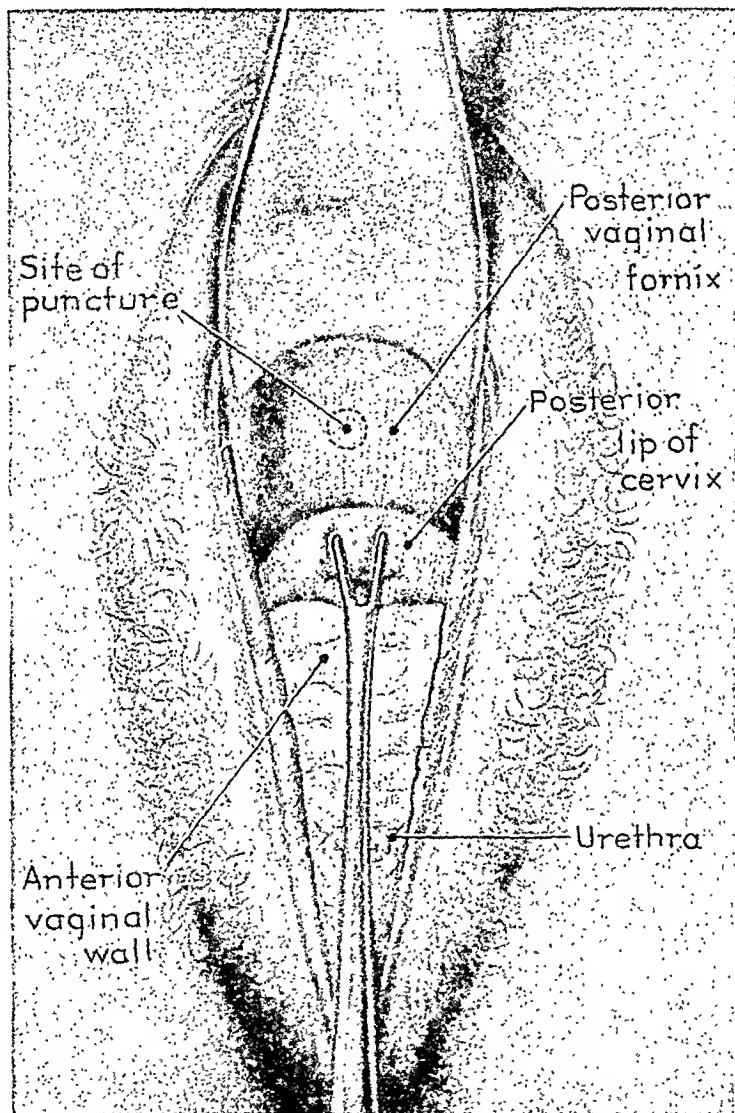


Fig. 3.—View of ballooned-out vagina with patient in knee-chest posture, showing site of puncture.

With the patient in the knee-chest position, the perineum is elevated with a Sims or other posterior vaginal retractor (Fig. 2). This permits air to enter the vagina and it balloons out, putting the mucosa of the posterior vault on considerable stretch. The spot at which the puncture is made is shown in Fig. 3. The novice is likely to puncture too close to the cervix, being afraid of injuring the rectum. If this mistake is made, the tip of the trochar ends in the retrocervical areolar tissue, and the cul-de-sac is not entered. If the puncture is made in the proper spot the stretched vaginal mucosa and peritoneum are easily perforated with a sudden quick puncture. As soon as the obturator is withdrawn there will be an audible in-rush of air if the tip of the cannula is in the cul-de-sac. If this

Dodd, Katharine, and Papoport, S.: Intravenous Alimentation of Infants, *J. Pediat.* 29: 758, 1946.

This report deals with experience acquired during the past year and one-half with the administration to infants by venoclysis of all, or the majority of, the needed elements of nutrition for periods up to fifteen days. Most of the children suffered from chronic or recurrent diarrhea and vomiting. The aim was to supply adequate fluid and salts, and at least maintenance amounts of calories and proteins.

A daily record of the total intake of fluids, saline, calories, and nitrogen as part of a careful plan is an essential prerequisite of such a program.

With the use of glucose, whole blood, plasma, and casein hydrolysate, a gain in weight may be achieved. Premature and very young infants require less saline in proportion to their body weight than do older infants.

The author warns of the danger of infection at the site of infection of casein hydrolysate. Thrombophlebitis and wound infection continue to be troublesome.

JAMES P. MARR.

Knop, Catharine: The Dynamics of Newly Born Babies, *J. Pediat.* 29: 721, 1946.

The author has studied the muscular energy or "dynamics" of 689 infants, who were examined twice during their eight-day stay in the hospital.

No definite correlation could be established between babies' weights and their dynamics.

The relation of the mothers' labor or sedatives received or the method of delivery to the grading of dynamics was inconclusive.

The author is of the opinion that the dynamic reaction determined at different times and even by different examiners remained essentially unchanged, supports the impression that a persistently inherent quality underlies reactions during the neonatal period.

JAMES P. MARR.

Salmon, George W., Forbes, Gilbert B., and Davenport, Harbert: Airblock in the Newborn Infant, *J. Pediat.* 30: 260, 1947.

The authors define airblock as that condition produced by escape of air from the normal respiratory pathways into tissues in which it is not normally present.

Since some of the terms used are long and awkward, they have substituted the abbreviation PIE for pulmonary interstitial emphysema, ME for mediastinal emphysema, and PT for pneumothorax.

The most reliable way of demonstrating PIE at autopsy is to enter the pleural spaces under water. Six cases are reported. Macklin was of opinion that the most likely and probably the most common sequence of events is as follows; air first passes through multiple and minute ruptures of the alveolar walls which border upon blood vessels, to form perivascular collections of air. From here air progresses along the blood vessels to reach the mediastinum. From the mediastinum the air may travel superiorly to produce cervical subcutaneous emphysema, or travel inferiorly to produce retroperitoneal emphysema and pneumoperitoneum. Also, from the mediastinum the air may travel into the interstitial tissue of the other lung, rupture into the pericardial sac, or rupture the mediastinal pleura to enter the pleural sac.

All patients showed evidence of anoxia. Amniotic fluid was stained with meconium in three cases. Two patients had intracranial hemorrhages, while one had a blood cisternal fluid but no autopsy of the head.

As treatment, the authors state that if the symptoms are mild, spontaneous recovery will likely ensure by increasing the oxygen concentration of inspired air.

If a large PT is present, aspiration is advisable. If a tension PT recurs a closed thoracotomy is performed and connected to a water trap so as to allow air to escape but not enter.

JAMES P. MARR.

Newborn

Bianchi, P.: Polycystic Ovaries in a Fetus, *Riv. Ital. di Ginec.* 28: 301, 1945.

P. Bianchi of the Medical School in Florence describes a case of bilateral polycystic ovary in a fetus in which follicles were developed to different stages as corresponding to findings in infancy and adolescence in which, however, maturing follicles had undergone regressive changes before reaching full maturity.

The ovary harbored primordial and primitive follicle and was studded with small cystic follicles, mainly lined by flat epithelium. The anterior lobe of the hypophysis showed in this case the histologic picture usually seen in a grown-up woman. Well-developed eosinophilic and basophilic cells were present, and interspersed with chromophobes. Basophiles were decidedly increased in number, and comprised 10 per cent of the cells which speaks in favor of the sexual function of basophilic cell activity. The thyroid gland also showed the features pertaining to adult life. The case presentation is completed by speculations as to the interrelationship of the maternal endocrine system to the endocrine system of the fetus.

GEMMA BARZILAI.

Editorial: What Is Epidemic Diarrhea of the Newborn? *New England J. Med.* 236: 115, 1947.

The American Academy of Pediatrics describes epidemic diarrhea in the following manner: an infant in the neonatal period who, previously well, suddenly passes one or more very loose or liquid stools combined with sudden abnormal loss of weight (after the period of initial weight loss) or one of the other symptoms associated with this type of diarrhea, such as vomiting, listlessness, drowsiness, refusal of feeding, short feeble cry, pallor, or elevation of temperature, should be immediately isolated and reported to the hospital authorities as a suspected case of infectious diarrhea.

The lack of knowledge regarding the etiology of epidemic diarrhea of the newborn adds to the confusion that obscures diagnosis in the individual case.

A control program would consist of periodic inspections of all hospital nurseries by the Board of Health to ensure that institutions providing care for the newborn were operating according to standard procedures. Overcrowding of nurseries, insufficient personnel, improper making of formulas and faulty sterilizing techniques emphasize the need for greater diligence on the part of those responsible for the care of newborn infants.

JAMES P. MARR.

Rubenstein, A. Daniel, and Foley, George E.: Epidemic Diarrhea of the Newborn in Massachusetts, *New England J. Med.* 236: 87, 1947.

It is the purpose of this discussion to review nineteen outbreaks of epidemic diarrhea of the newborn as reported to the Massachusetts Department of Public Health from 1935 to 1945. In the 258 cases reported, eighty-five patients died, giving a case mortality of 33 per cent.

The etiology and mode of transmission of epidemic diarrhea in the newborn nurseries where these outbreaks occurred revealed many inadequacies. Overcrowding, insufficient personnel, general use of a common rectal thermometer, and inadequate supervision of formula making were frequently encountered.

In several outbreaks, apparently identical organisms were isolated from sick and healthy infants, nursery personnel, and formulas. The presence of Group D, streptococci in the throats of infants with epidemic diarrhea of the newborn suggests that, as a result of poor nursery techniques, infants may be exposed to organisms that are normally found in the human intestinal tract.

JAMES P. MARR.

Lewis, J. M., Bodansky, O., Lillienfeld, M. C. C., and Schneider, H.: Supplements of Vitamin A and of Carotene During Pregnancy, Their Effect on the Levels of Vitamin A and Carotene in the Blood of Mother and of Newborn Infant, *Am. J. Dis. Child.* 73: 143, 1947.

Seventy-four women were given 10,000 units of vitamin A or of carotene during the last few months of pregnancy in order to determine whether these supplements would prevent the fall of vitamin A in the blood which normally takes place in the last trimester.

Dark adaptation tests are now being carried out on a large group of pregnant women to ascertain whether the low levels of Vitamin A are associated with poor dark adaptation which, as had been shown in previous studies on infants and children, becomes detectable when vitamin A deficiency is of moderate or profound degree. The authors noted that at present there is no evidence that low concentrations of vitamin A in the blood of pregnant women are associated with clinical manifestations of vitamin A deficiency.

The result of this study indicates where vitamin A, which is supplemented in the aforementioned dosage, brought about a maintenance of good levels of vitamin A during the last phase of pregnancy.

JAMES P. MARR.

Fouracre-Barns, H. H.: Retrodisplaced Gravid Uterus, *Brit. M. J.* 4491: 169-172, 1947.

The author reviews 66 cases with a retrodisplaced gravid uterus. He makes a plea for conservative treatment of the sterile woman with a retroversion and suggests that operative correction of a retrodisplaced uterus for a previous abortion is unwarranted.

In the writer's experience incarceration occurs between the thirteenth and seventeenth weeks of pregnancy, and he discusses two cases of sacculation of the incarcerated gravid uterus. The cardinal symptoms of incarceration was sudden onset of urine retention with lower abdominal pain. His conservative treatment includes gradual bladder decompression, watch-spring pessary, urinary antiseptics—with emphasis upon posture and pessary for those not incarcerated.

C. E. FOLSOME.

Aviles, V., Manuel: Our Experience With Cardiac Patients During Pregnancy, *Obstet. y Ginec., Latino-Am.* 4: 571-584, 1946.

In the author's maternity hospital there were 472 cases of cardiac disease among 52,485 pregnant women during the last ten years. This is an incidence of 9 per cent. There were forty-nine instances of heart failure and among these women five died. In spite of the many cases of cardiac failure which occurred during pregnancy, the total mortality for the women with valvular disease was only 2.91 per cent. The author emphasizes that the capacity of the muscle is not the only important consideration in the care of patients with heart disease. The occurrence of failure can be avoided by instituting treatment early. This consists of proper diet, rest and intermittent digitalization. Therapeutic abortion is rarely indicated in cases of heart disease and it should be reserved for patients with serious and repeated accidents such as total arrhythmia and auricular fibrillation. There were only five abortions in this series.

J. P. GREENHILL.

Garcia Huidobro, M., and Paredes, L.: The Friedman Reaction in the Cerebrospinal Fluid and Its Importance in the Diagnosis of Hydatid Mole, *Bol. Soc. chilena de obst. y ginec.* 11: 31-34, 1946.

The authors report a series of 13 Friedman tests performed on the cerebrospinal fluid. Of four women with hydatid mole the test was positive in three and negative in one. The authors attribute the negative result to the small amount (5 c.c.) of spinal fluid used for the test. In three cases, Friedman tests on the spinal fluid were performed two, ten, and forty-eight hours, respectively, after expulsion of the mole, and in all three the tests were positive. However, in two women tests were carried out on the fourth and seventh days respectively

Pregnancy

Ingerslev, Magens, and Teilum, Gunnar: Biopsy Studies on the Liver in Pregnancy. II. Liver Biopsy on Normal Pregnant Women, *Acta obst. et gynec. Scandinav.* 25: 352-360, 1945.

The authors, working at the Lying-In Department of Rigshospital, Copenhagen, used Iversen and Roholm's technique for biopsy of the liver (performed by the latter on more than 1,000 cases) to obtain liver aspiration biopsies on 17 normal pregnant women. The purpose of their study was to re-evaluate the so-called "pregnancy liver" by histologic studies on such specimens.

Ingerslev and Teilum observe that the massive histologic changes in the liver reported by Hofbauer, in 1908, during normal pregnancy could not be confirmed by either post mortem or aspiration biopsy histologic studies. Accordingly, they conclude that the connotation "pregnancy liver" cannot be maintained as an histological concept.

The writers close their article with the observation that while several physiological and biochemical findings indicate that pregnancy is associated with certain changes to the intermediate metabolism localized to the liver, there are no pathophysiological reasons to maintain the concept of the "liver of pregnancy." One chart and two photomicrographs accompany the article.

C. E. FOLSOME.

Ingerslev, Magens, and Teilum, Gunnar: Biopsy Studies on the Liver in Pregnancy. III. Liver Biopsy in Albuminuria of Pregnancy, Eclampsism and Eclampsia, *Acta obst. et gynec. Scandinav.* 25: 361-376, 1945.

In this concluding paper of a triad of articles preceded by two others concerned with biopsy studies of the liver in normal nonpregnant and pregnant women, the authors focus their attention upon utilization of these same methods for the histopathologic study of the liver in three types of toxemias, pre-eclampsia and eclampsia.

In their series of eight cases of albuminuria of pregnancy, and in six cases of pre-eclampsia, neither the clinical examination nor histologic examination of the liver, removed in biopsy, revealed any definite signs of a liver lesion. The histologic studies observed in these conditions were quite in keeping with that obtained in the control material for the normal nonpregnant and the normal pregnant woman's specimens.

Among the five cases of eclampsia two patients showed a perfectly normal histologic picture, while one presented some slight degenerative changes, and two showed characteristic peripheral precipitation of fibrin with necrosis and hemorrhage in an otherwise perfectly normal liver tissue. Thus pronounced histologic changes have been demonstrated only in patients with fully-developed eclampsia. Even severe histopathologic changes are found not to be incompatible with patient survival.

The writers conclude that the fibrinous precipitates were taken to constitute the essential feature in the pathologic picture—and perhaps also the central factor in the production of the convulsive seizures. There are three tables and five photomicrographs accompanying the article.

C. E. FOLSOME.

De Giorgi, Luigi: About So-Called Chorionic Infiltration, *Arch. di ostet. e ginec.* 51: 207, 1946.

De Giorgi reviews the material of the University of Naples related to abnormalities of placentation. Microphotos of accrete placenta, vesicular mole, infiltrative mole, and chorion-epithelioma are presented. Data related to differential diagnosis of these entities are discussed. The existence of chorionic infiltration as a peculiar entity, different from the above-named hyperplastic and neoplastic aspects of placentation, as formerly advanced by Poso and Miranda, is denied by De Giorgi on the basis of the material he had the opportunity to study.

GEMMA BARZILAI.

blood fails to clot and fibrinogen is often decreased in concentration or is even absent. (6) There are two literature reports that the "neutralizer" in serum (therefore antithromboplastin) is markedly decreased in eclamptic patients.

Schneider concludes that antithromboplastin is the inactivator of the toxin, thromboplastin and while actual proof is lacking there is no evidence to the contrary that thromboplastin might be the cause of toxemia of pregnancy.

C. E. FOLSOME.

Fertility, Sterility

Murless, Bryan C.: A Review of the Present Position of the Investigation of Sterility and Infertility in the Female, South African M. J. 20: 788-793, 1946.

The author reviews, in superb English and in a singularly well-organized manner, the methods of investigation of female sterility. He re-evaluates the older approaches to this problem but adds much new data, presently available only in scattered texts and recent articles, in such a fashion as to clearly summarize the knowledge on this phase of gynecology up to 1946.

He concludes that the investigation of sterility is essentially negative in character, as the factors which determine fertility in the female are so varied. His cardinal object is to eliminate the known causes of infertility. Murless agrees that actual proof of fertility is not obtainable until conception has taken place.

C. E. FOLSOME.

Rommer, J. Jay: Psychoneurogenic Causes of Sterility and Their Treatment, With Preliminary Remarks on Allergic Sterility, West. J. Surg. 55: 278, 1947.

To the ancient Greeks and Romans and to the others of lesser historical stature, the author turns to observe the incantations and religious practices designed to alleviate the sterile state. He considers the psyche in relation to sterility under two broad classifications: psychogenic sterility and neurogenic sterility.

Mental disorders, fears or anxieties, depressions and psychic trauma, sexual perversions and frigidity may disturb the normal pituitary ovarian endometrial cycle. A heavy outpouring of adrenalin, associated with some of these psychic states, may produce castration-like changes in the anterior pituitary.

The Rubin kymograph was set up with a 15 c.c. balloon in the vagina to record vaginal contractions during a manually induced orgasm. It was observed that the vaginal muscles become more contractile, while the uterus remains quiescent. Allergy and associated conditions may cause sterility by inducing an edema in the cervix and endometrium.

WILLIAM BICKERS.

Brooks, Matilda Moldenhauer, The Mechanism of Fertilization of Eggs, Growth 10: 391-410, 1946.

Brooks, using the eggs and sperm of *Arbacia*, *Asterias* and *Chaetopterus*, began her studies upon the hypothesis that fertilization depends upon the attainment of the correct redox potential (which is a measure of the tendency a substance has to give up or to take up electrons) of the egg. The author noted a difference in potential between egg and sperm and the degree of this difference varied with the species. In some cases as in *Arbacia* it was considerable, whereas in other cases it was very slight as in *Asterias*.

The electromotively active enzyme systems required "activation" to produce the beginning of development. This meant that the concentration of oxidants and reductants must be more nearly equalized so that the electron shift could take place at an optimum rate, thereby releasing the necessary energy. In some cases as in *Asterias*, only a slight shift in potential was required. In others as *Arbacia*, there was a considerable change. This would explain why *Arbacia* eggs have a large rise in oxygen consumption on fertilization and *Asterias* eggs do not. The fact that eggs and sperm contain different proportions of these oxidants and reductants cause them to react.

after expulsion of the mole and the tests were negative. Tests were performed in four control women without hydatid mole and all the tests were negative. From their study the authors conclude that Friedman tests performed on 10 c.c. of spinal fluid are of great assistance in the diagnosis of hydatid mole.

J. P. GREENHILL.

Cabrera, S. H.: Some Considerations of Hydatid Mole, *Bol. Soc. chilena de obst. y ginec.* 11: 39-55, 1946.

At the San Borja Maternity, among 77,947 pregnancy cases, there were 15,142 abortions and 94 hydatid moles. The hydatid moles were discovered in pregnancy as follows: one month, 1; two months, 22; three months, 36; four months, 23; five months, 6; six months, 3; and seven months, one. Most of the moles were expelled spontaneously at the third and fourth months, and the majority were not expelled completely. Hemorrhage was usually severe enough to require blood transfusion. The total mortality was 0.94 per cent.

The authors emphasize that as soon as the diagnosis is made, the uterus should be emptied. In not a single case of the authors has a chorionepithelioma developed. This has been proven both by repeated clinical examinations and by biologic gonadotropin tests.

J. P. GREENHILL.

Toxemia

Parviainen, Sakari: An Investigation of the Manifestation of Precursory Symptoms of Nephrogestosis and Their Importance for the Prognosis of Parturition, *Ann. Chirurg. et Gynec. Fenniae* 35: Supplement 1, 1946.

The author presents an analysis of the 5,557 women who received antenatal care at the Maternity Center in Helsinki in the years 1942 and 1943. Of this number, 1,418 showed symptoms of nephrogestosis or signs of a potential outbreak of the disease. The diagnosis of this condition was based on the finding of any or all of the following: albumin in the urine, elevated blood pressure, and edema. Attention is called to the fact that edema is the first finding which suggests nephrogestosis; high blood pressure usually makes its appearance shortly thereafter, and it is not until much later that albumin appears in the urine. Of the 1,418 cases, sixty-six were classified as pre-eclampsia, and eight actually developed eclamptic convulsions. The author admits that his statistical analysis is somewhat confused because of the difficulties imposed as a result of the war. However, it is interesting to note that there was a significant fall in the number of cases of nephrogestosis and, to a lesser extent, in the number of cases of actual eclampsia during the war years.

It is suggested that, even though apparently unnecessary work will be involved, if we are to reduce substantially the number of cases of nephrogestosis occurring in parturition, the patient must be seen more frequently prenatally, and careful check made for the presence of elevated blood pressure, edema, and albuminuria.

HERBERT J. SIMON.

Schneider, Charles L.: The Active Principle of Placental Toxin: Thromboplastin; Its Inactivator in Blood: Antithromboplastin, *Am. J. Physiol.* 149: 127-129, 1947.

Schneider believes he has demonstrated that the toxin from tissue extracts, especially placental extracts, possessing such toxin, long suspected as a causative agent in the toxemia of pregnancy, is thromboplastin and that its lethal effect depends on intravascular clotting. The author lists six reasons he believes support the possibilities that thromboplastin is actually the causative agent in toxemia of pregnancy. (1) The anatomic lesions of eclampsia are consistent with the underlying lesion being multiple thrombosis. (2) The concentration of antithromboplastin of the blood increases during pregnancy. (3) Anatomic relationship does not preclude that thromboplastin from the placenta can enter the maternal blood stream. (4) Pregnant animals are more sensitive to thromboplastin than are non-pregnant animals. (5) In the few recorded moribund toxemia patients the blood clotting time is prolonged else the

mg. of estrone sulfate, and 18 mg. of diethylstilbestrol, over a period of 8 years. This same patient had a positive diagnosis of endometrial hyperplasia two years prior to the discovery of her malignancy. The authors believe that this is the first report on the occurrence of endometrical cancer in a women undergoing prolonged treatment with estrogen.

WILLIAM BERMAN.

Howe, Martha E., and Jennings, Mary A.: Intrauterine Irradiation, A Modification of the Radiumhemmet Packing Method, *J. A. M. Women's A.* 2: 83, 1947.

In cases of cancer of the uterine body which are not treated surgically, one should deliver a maximal radiotherapeutic dose to the entire endometrium, and as deeply as possible into the uterine wall. In the irregular and distorted uterine cavity it is not possible to predetermine the location or extent of mucosal or myometrial extension.

Since radium needles in tandem are not likely to deliver efficient radiation, various methods of applicator distribution have been tried. In 1939 the Radiumhemmet group (Sweden) began to pack the uterus with numbers of tubular steel casings containing radium salt. This type of treatment has resulted in a 20 per cent improvement in five-year results in those cases which had treatment by radiation alone.

Howe and Jennings, of the New York Infirmary, have devised and used a new type of applicator. It is shaped like an olive pit, 20 mm. in length and 8 mm. in maximum diameter (one size only). It is closed by a screw cap bearing an eyelet for identifying tags. The shape permits penetration into the uterine cornu, close packing against neighboring applicators, and the shape minimizes weak radiation at the ends, since applicators can overlap. About ten applicators fill the uterus and cervical canal (dilatation of the cervix is maintained by the application in situ).

After insertion the patient is x-rayed to be sure that perforation has not occurred, and to demonstrate good distribution of applicators. A dose of 1,000 gamma roentgens is delivered at a depth of 1.5 cm. at each of three treatments, with one supplemental treatment to the vaginal vault and cervical portio by a vaginal applicator. The total dose to the uterus and vagina will vary from 3,300 to 6,000 milligram hours, depending on the size of these cavities. The total presumptive tumor dose, however, should be about the same in any case; about 3,000 gamma roentgens at 1.5 cm. depth and about 12,000 to 15,000 gamma roentgens at the endometrium. Experience with this method is limited as yet, and does not warrant conclusions as to its worth.

IRVING L. FRANK.

Anatomy

Swenson, Paul C.: Anatomic Variations in the Female Pelvis: The Caldwell-Moloy Classification, *Radiology* 827: 1947.

In an editorial, Swenson discusses the paper of Nicholson and Allen (*Lancet* 2: 192, 1946). These authors have criticized the Caldwell-Moloy classification for lack of precision, and for limitless subclassification and multiplication of types. They seek to disprove that anthropoid and android pelvis are associated with narrow outlets, or that the android pelvis is associated with difficult labor. Caldwell and Moloy, however, did not present these as constant relationships. A large pelvis may not be dystocic whatever its shape, whereas in pelvis of normal or borderline size, the pelvic form may be of prime importance.

Nicholson and Allen believe that all pelvic deformities are due to malnutrition in childhood, but Swenson indicates that nutrition affects only the general size of a predetermined (hereditary or hormonal influences) type. Emphasis on size alone will probably not be as valuable as the dynamic method of Caldwell-Moloy, which in its size-shape analysis has been of great aid to obstetricians.

IRVING L. FRANK.

The formation of acid upon fertilization of some eggs, whether by sperm or artificially, is an important factor and fitted the above theory that a change in pH of the egg produced a change in the redox potential. The increased production of carbon dioxide or other acids in the egg, caused by such various methods as sperm, hypertonic and hypotonic solutions, pricking, shaking or ultra violet light; was assumed by the author to be the cause of initiating development owing to changes in redox potential so produced.

When eggs were placed in sea water or modified sea water, they lowered the Eh and the pH (hydrogen in concentration). This lowering was more pronounced in modified sea water than in sea water. The redox potential of different species of eggs was different and changed with stages of development.

In conclusion Brooks states there was a definite correlation between the rate of oxygen consumption of unfertilized and fertilized eggs and the redox potential of these eggs. The three groups of eggs studied illustrated the hypothesis that fertilization of the egg depended upon the correct ratio of oxidants to reductants of the enzyme systems. C. E. FOLSOME.

Michelson, Lewis: Azoospermia: An Analysis of 146 Cases, J. Urol. 57: 512-518, 1947.

Michelson presents an excellently documented and detailed analysis of 146 cases of azoospermia which had been most carefully studied.

In sixty-nine cases, 47 per cent, the etiology was determined; in seventeen cases, 11 per cent, the cause could be shown only unilaterally; in sixty patients, 41 per cent, this factor could not be determined.

The most frequent cause of degeneration of the spermatogenic cells was cryptorchidism, occurring in twelve cases, 8 per cent, of the series. Mumps orchitis degenerative changes were seen in nine cases, 6 per cent of the series. The most frequent disease causing obstruction of the vaso-epididymal duct was gonorrhea. This occurred in thirty-five cases, or 24 per cent of the series.

Absence of both vasa was found in four cases. Testicular biopsy is deemed, by Michelson, as essential in diagnosis and determining treatment of azoospermia. His results of treatment were poor. He has seen not a single case show improvement after hormone therapy. In his hands only surgical measures have been successful and these are among the obstructive azoospermic cases. Three of eight cases showed sperm postoperatively and in two of these three cases the wife became pregnant. C. E. FOLSOME.

Labor

Strouse, Solomon, and Drabkin, Charles: Hyperthyroidism in Pregnancy Treated With Thiouracil, J. A. M. A. 131: 1494, 1946.

The authors report a case of a 31-year-old primigravida with symptoms of hyperthyroidism following a thyroidectomy six years previously. The patient developed dyspnea, palpitation, tachycardia, and edema, and was placed on Lugol's solution, digitalis and sedatives with only fair results. She was then placed on thiouracil 0.6 Gm. daily and in one week she was feeling fine. She entered the hospital with ruptured membranes and a breech presentation. She was delivered by a low cervical section under spinal anesthesia. The post-operative course was uneventful. The baby gave the impression of being hypothyroid. The baby's subsequent development was perfectly normal. WILLIAM BERMAN.

Malignancies

Fremont-Smith, Maurice, Miegs, Joe V., Graham, Ruth M., and Gilbert, Helen H.: Cancer of the Endometrium and Prolonged Estrogen Therapy, J. A. M. A. 131: 805, 1946.

The authors review the literature with reference to the carcinogenic effect upon the uterus and the breast with the continued use of estrogens. The authors report a case of endometrical cancer in a woman undergoing prolonged treatment with estrogen.

Necrology

HENRICUS JOHANNES STANDER, M.S., M.D., professor of obstetrics and gynecology at the Cornell Medical College and chief of the New York Lying-In Hospital, died at his home in Searsdale, N. Y., on May 2, 1948, at the age of 53 years. Born in South Africa of Boer and English ancestry, he studied chemistry at the South African College and then at Harvard University, having arrived in the United States in 1913. He next was associated with the School of Mines of the University of Arizona, where he obtained his M.S. degree in 1916, and subsequently was a consulting chemist for the Hercules Powder Company at Wilmington, Del. Later, Dr. Stander entered the Yale Medical School and received his M.D. degree in 1921. He then became a member of the Department of Obstetrics of Johns Hopkins under the late Dr. J. Whitridge Williams. Subsequently he edited and enlarged Williams' well-known textbook on obstetrics and was the author of many articles in American medical journals. An honorary degree of Doctor of Medicine was awarded to him by the University of Dublin a year ago. Dr. Stander was a Fellow and member of the leading obstetrical societies of this country and for many years a member of the Advisory Medical Board of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

JOSIAH MORRIS SLEMONS, A.B., M.D., obstetrician and gynecologist, died in Los Angeles, Calif., on April 30, 1948, at the age of 71 years. A graduate of Johns Hopkins in 1901, he served there as instructor and associate professor of obstetrics, 1904 to 1913; as professor of obstetrics at the University of California, 1913 to 1915; as professor of obstetrics and gynecology in the Yale University Medical School, 1915 to 1920. During 1917, he was in charge of the survey of obstetrics in France under the sponsorship of the Red Cross and subsequently was a Major in the U.S.A. Medical Corps. He was the author of several books and numerous articles published in the JOURNAL. He lived in retirement at Los Angeles for several years.

Item

The following is inserted at the request of the Cutter Laboratories:
For Immediate Release

Berkeley, Calif.
May 6, 1948

Superseding our air mail release dated May 5, 1948 is the following statement from Dr. R. K. Cutter, president, of Cutter Laboratories. "Contamination has been found in another and entirely different glucose solution, dextrose 10 per cent in Ringer's, according to an announcement made today by Dr. R. K. Cutter, president, of Cutter Laboratories. The company is cooperating with the Food and Drug Administration, and is requesting the assistance of health departments throughout the country, in immediately recalling from hospitals Cutter's entire line of dextrose and other solutions for mass intravenous injection. Company officials believe that discovery of this new contamination makes questionable the use of any product produced in their intravenous solutions department until this entire contamination difficulty is solved. The other products produced in this department are concentrated dextrose, distilled water, sodium citrate, normal saline solutions in 50 and 100 c.c. bottles, as well as all flasks supplied by Cutter for community blood and plasma banks."

Announcement

In view of the many manuscripts submitted for publication in the JOURNAL, the number of pages in each issue will be increased to 200, beginning with the July number.

does not occur, it is obvious that it is not in the peritoneal cavity and that there is some adherent structure in the cul-de-sac. The latter possibility can usually be avoided by a previous careful bimanual examination.

The sterile culdoscope is then introduced through the cannula. It is to be noted that the culdoscope which comes in contact with the viscera never touches the vaginal mucosa, thus reducing the possibility of infection to nil.

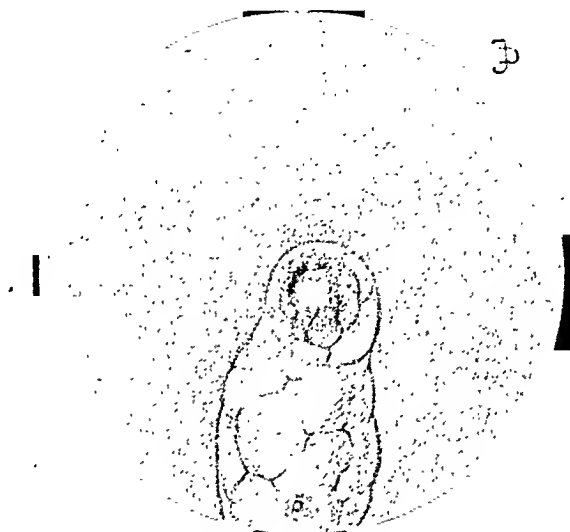


Fig. 4.—Culdoscopic view of normal ovary with corpus luteum.

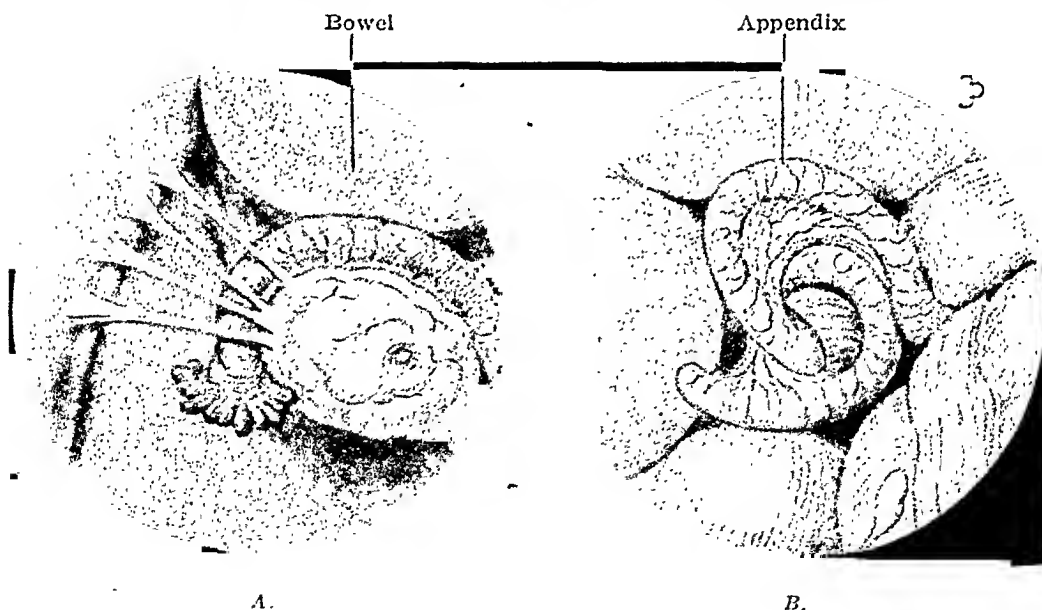


Fig. 5.—A. Culdoscopic view of ovary and tube. B. Culdoscopic view of appendix.

The uterus, tubes, ovaries, broad ligaments, uterosacral ligaments, infundibulopelvic ligaments, rectal wall, sigmoid, small intestines, and often the cecum, appendix, and even the ureters can be visualized. The culdoscope may be moved from side to side and rotated as necessary. The direction of visibility through the lens is indicated by a marker on the eyepiece. The viscera can be moved so as to come into view by manipulation with the tip of the culdoscope, by movement of the volsellum on the cervix or, better still, by

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making manual pressure at various points in the suprapubic region. Occasionally, if the lens is introduced cold, it may become hazy, due to the body heat. Therefore, it is well to dip it in warm water and then wipe dry just before inserting it into the cannula. The lens magnifies structures to some degree, depending upon the distance it is from the object. As the tip of the culdoscope is drawn away from the object, a larger field is visualized and the individual structures seem smaller. Figs. 4, 5, and 6 are actual drawings by the artist of culdoscopic views of normal or nearly normal viscera.

If the object of the culdoscopy is to inspect the tubes carefully to determine points of obstruction, a self-retaining screw tip cervical cannula is introduced in the cervical canal. This is attached by means of rubber tubing to a syringe filled with a weak solution of methylene blue. As the fluid is forced in, distention of the tube can be seen proximal to the point of obstruction. If the tubes are patent, methylene blue can be seen dripping from the fimbriated ends.

On completion of the examination the culdoscope is withdrawn, but the cannula is left in place as the patient assumes the lateral recumbent position. Pressure is made by an assistant on the abdomen until the air is exhausted from the abdominal cavity. The out-rushing of air is quite audible. The wound in the cul-de-sac is not sutured. Fig. 7 shows wound in the cul-de-sac from within the abdomen two days after culdoscopic examination.



Fig. 6.—View of ureter which can occasionally be visualized.

Discussion

The greatest indication which we have found for culdoscopy is to gain more information in cases in which the history and/or pelvic examination suggest tubal pregnancy. Of the fifty-six cases of culdoscopy reported here, 37 were done for this purpose. Ectopic gestation is more often overlooked and more often diagnosed when not present than any other serious pelvic lesion. I doubt whether there is a gynecologist or obstetrician who has not made such errors. A correct diagnosis is imperative. Fearing the consequences of failure to diagnose an existing tubal pregnancy, many abdomens are explored, only to find no abnormality or a minor lesion for which surgery is not neces-

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sary. In the typical case the diagnosis is simple, but a large percentage of tubal pregnancies are far from typical as to history and pelvic findings. On our Negro service we see great numbers of women who prove to have salpingitis, but the history and pelvic findings are so suggestive of ectopic gestation that we cannot dismiss them with a clear conscience. Of the thirty-seven patients who were culdoscoped because the history and/or pelvic findings were suggestive of tubal gestation, a diagnosis of tubal pregnancy was made in five instances.

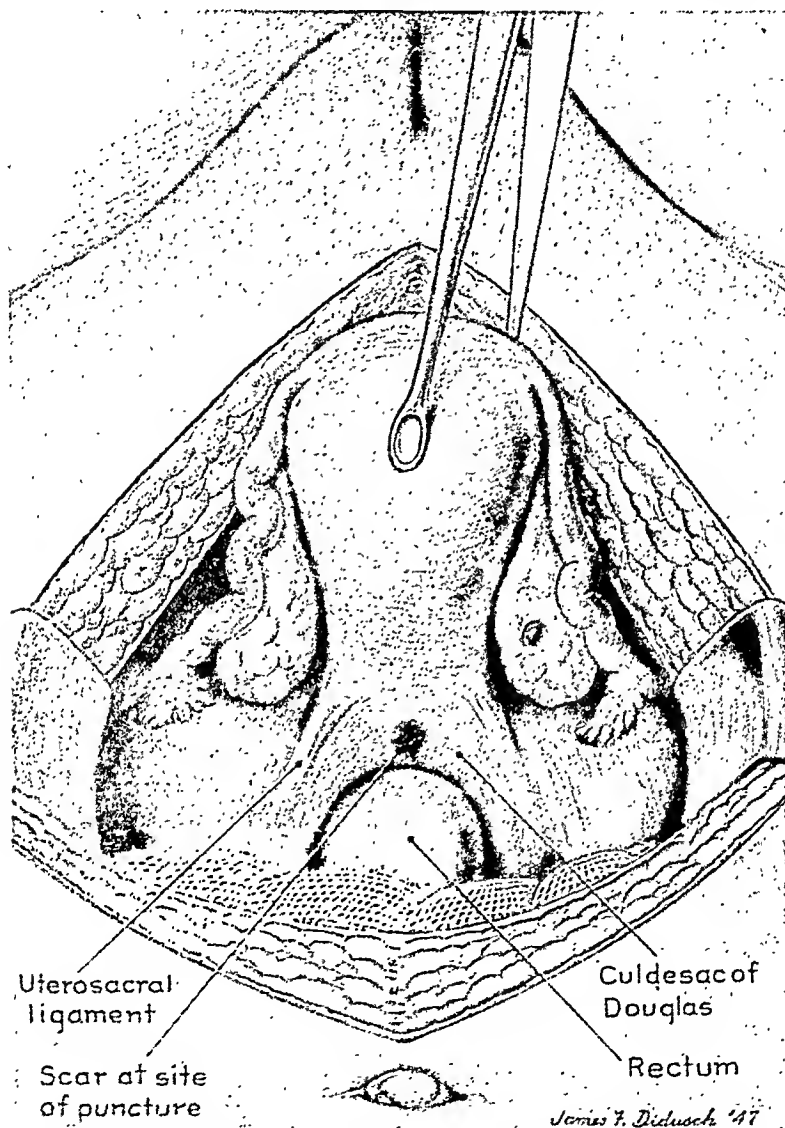


Fig. 7.—View of cul-de-sac wound two days after culdoscopy.

In each instance operation proved the culdoscopic examination to be correct. None of the thirty-two cases in which tubal pregnancy was excluded was found to have it by subsequent operation or observation. We do not mean to infer that in all of the thirty-two cases laparotomy would have been necessary to exclude tubal pregnancy with certainty. In some instances simple observation in the hospital would have eventually ruled it out; in others a pregnancy test.

The differential diagnosis between salpingitis and endometriosis may, at times, offer considerable difficulty. To make such a differentiation may be of great value, for our attitude toward surgery in the two conditions is quite different. In young women the desirability of the preservation of the childbearing function is the aim in both conditions. This is best accomplished in most instances by nonoperative treatment when dealing with salpingitis. With endometriosis, on the other hand, early conservative surgery may permit future pregnancy, while delay in surgery may make conservative surgery impossible. The culdoscopic pictures in both conditions are quite characteristic, and the differentiation is easily made unless the cul-de-sac is obliterated by adhesions.

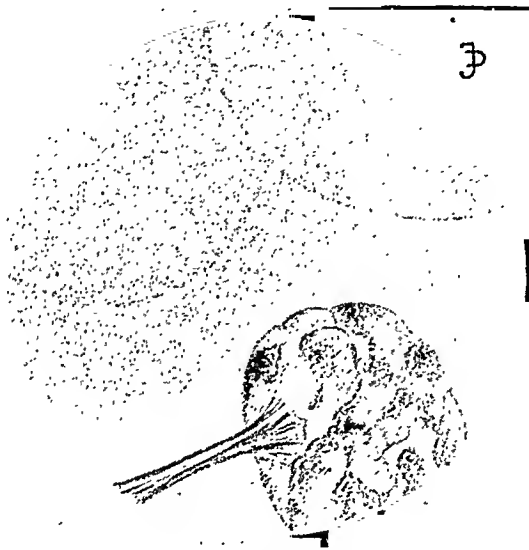


FIG. 8.—Culdoscopic wound of ovary with small blood clots in case of ruptured tubal pregnancy. The dark area in the background is old blood out of focus.

The differentiation between very early acute salpingitis and acute appendicitis is not always a simple matter. To carry out the proper treatment such a differentiation is essential without too much delay. A mistake in judgment may result in an unnecessary operation or rupture of the appendix. Although acute inflammatory conditions within the abdomen contraindicate peritoneoscopy, culdосcopy can be quite harmlessly done. In the very early stage of acute salpingitis there are few adhesions, and the tubes are easily visualized. Not infrequently the appendix can also be seen, but in any event enough information can be obtained in each instance to make the diagnosis with certainty.

Although we have not used culdосcopy for that purpose in this series of cases, we can conceive of circumstances under which it would be very advantageous in differentiating between Neisserian and tuberculous salpingitis.

Ovarian enlargement of lesser degree may give the gynecologist the greatest concern. To remove a follicular cyst which would probably ultimately disappear spontaneously is to perform unnecessary surgery. To permit a small neoplastic cyst to remain in the pelvis may have ultimate serious consequences. Watchful waiting is justifiable for a time, and the spontaneous disappearance of the cyst

curettage, or colpotomy would have led us to the right diagnosis. However, as a result of culdoscopy we were able to discharge many of these patients from the wards promptly and with safety, thus releasing much needed hospital beds.

It is only fair to say that in many instances simple colpotomy would have made or ruled out the diagnosis of tubal pregnancy with reasonable certainty. However, it is on occasion quite impossible to detect definitely an unruptured tubal pregnancy or even an early tubal abortion by colpotomy. On two occasions in the past simple colpotomy mislead one of us (R. W. T.) to interpret a small amount of blood in the cul-de-sac as indicating tubal pregnancy, when the bleeding actually arose from a corpus luteum and undoubtedly would have subsided spontaneously without serious effect. With culdoscopy such a satisfactory view of the tube and ovary is obtained in most instances that the exact origin of the bleeding can be detected and a correct decision for or against laparotomy made.

Salpingitis in some form was found to be the condition simulating tubal gestation in eighteen of the thirty-seven cases. There were three cases of retained placental tissue and one early intrauterine pregnancy. Three follicular retention cysts and one large corpus luteum were found. There was one case of endometriosis, and in five cases we were forced to make a diagnosis of unexplained abdominal pain. Subsequent operation or observation of these cases substantiated culdoscopic observations.

Other circumstances under which culdoscopy is useful are numerous.

Lower abdominal pain which is atypical in character and which is not satisfactorily explained by the usual gynecologic or other physical examination is one of the common problems which confronts every gynecologist. Often the conscientious gynecologist decides with the greatest difficulty whether a given patient warrants an exploratory laparotomy or whether she should be placed in the psychosomatic class. Mistakes are not infrequent in both directions. Many a psychoneurotic woman is subjected to an unnecessary exploratory laparotomy, and often a patient with real but undetectable pathology is classified as neurotic. In this series of patients there is one who had been examined by two excellent gynecologists only to be told that there was no organic basis for her complaint of left lower quadrant pain. One of us (R. W. T.) examined her and found her pelvis quite normal to palpation. Her complaint was so definite that we were loath to put her in the psychosomatic group. Finally, we culdoscoped her and found the left ovary adherent to the sigmoid by an endometriosis process. On bimanual examination the normal sized ovary moved perfectly freely with the sigmoid and was thought to be free of disease. Removal of the left ovary completely relieved the left lower quadrant pain.

In cases of severe dysmenorrhea there always exists the possibility of very early endometriosis, undetectable by bimanual palpation. Visualization of the ovaries and pelvic peritoneum may make a diagnosis and thus permit early conservative surgical treatment,

In certain endocrine disturbances, such as functional bleeding, functional amenorrhea, ovarian dwarfism, and ovarian agenesis, exact knowledge of the anatomy and, to some degree, the physiologic condition of the ovaries can be learned only by culdосcopy or exploratory laparotomy. The advantages of culdосcopy are apparent. The knowledge thus gained may prove of value in therapy, and subsequent culdосcopic examinations may prove valuable as a check on therapy.

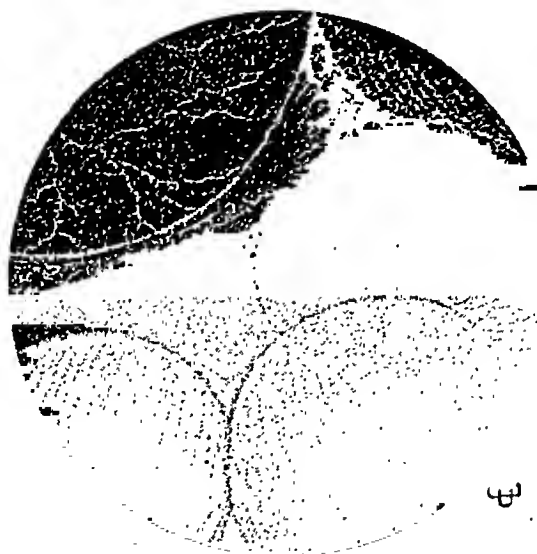


Fig. 11.—Culdосcopic view showing portion of an ovarian cyst with tube stretched over it.

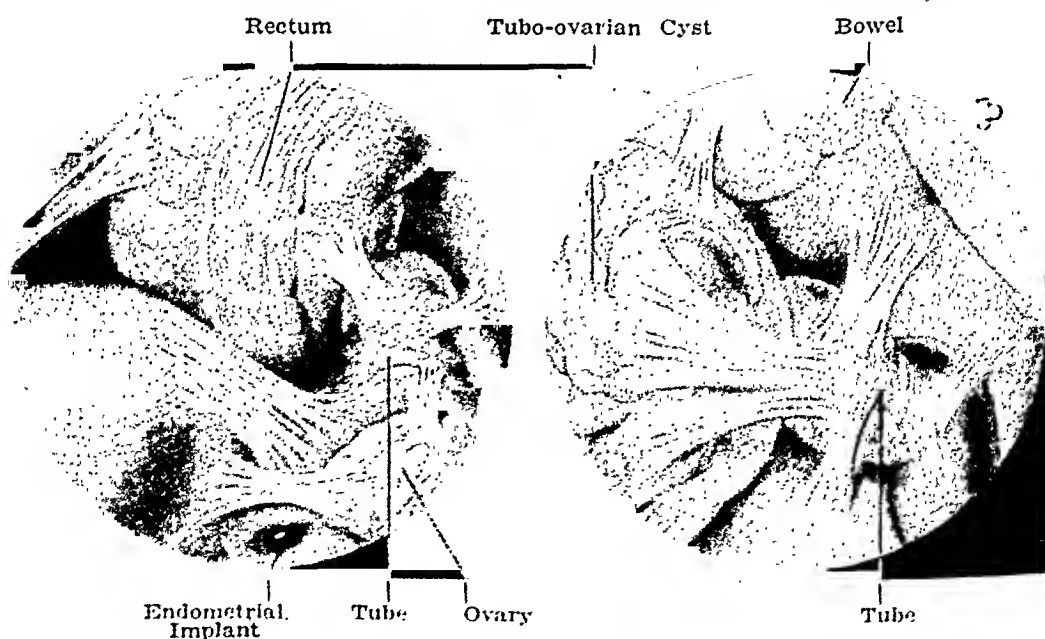


Fig. 12.—Culdосcopic views of adnexa in case of residue of endometriosis and of pelvic inflammatory disease.

Finally, the culdосcope is of value in investigating sterility. Just how valuable it will prove to be will become apparent as we extend our experience with it. Much information can be gained about the condition of closed tubes

settles the question quite satisfactorily. There are some cases, however, in which the ovarian enlargement persists even when it is not due to neoplasm. Usually the differentiation between a retention cyst or cystic ovary and a neoplasm is easily made through the culdoscope.

Not infrequently, in our experience, postmenopausal bleeding is not satisfactorily explained on examination of curettings. It is disturbing to have the bleeding recur in some of these women, and there remains the possibility of an early nonpalpable ovarian or tubal neoplasm. This can be determined with greater assurance by culdoscopy.

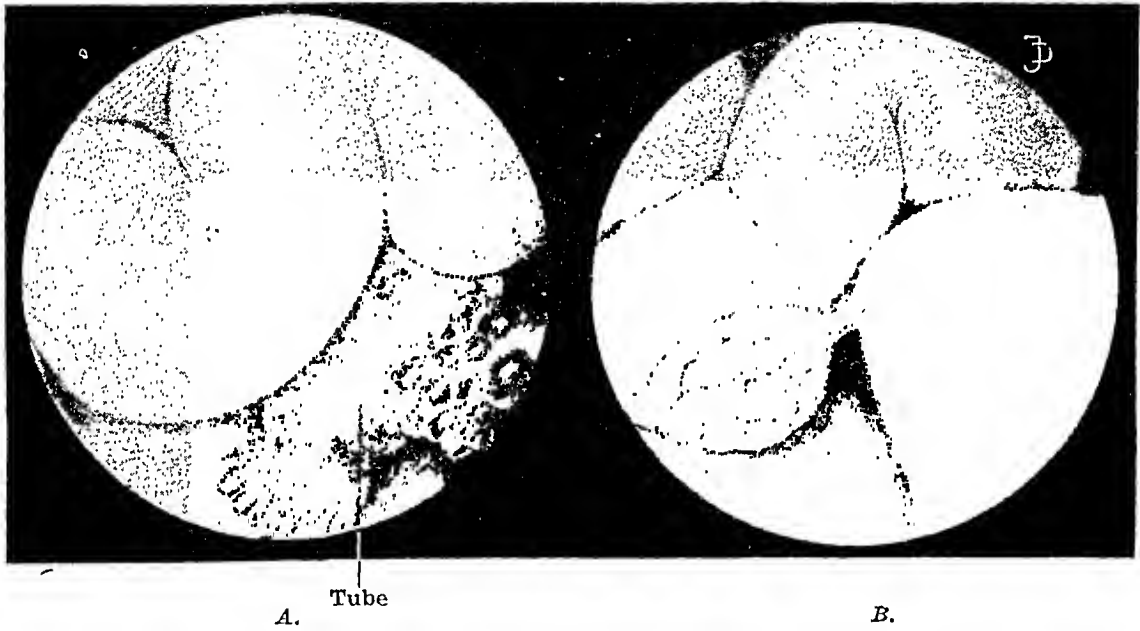


Fig. 9.—A. Tubal pregnancy with tubal abortion. B. Normal ovary on opposite side. The tube on this side was previously removed because of a tubal pregnancy.

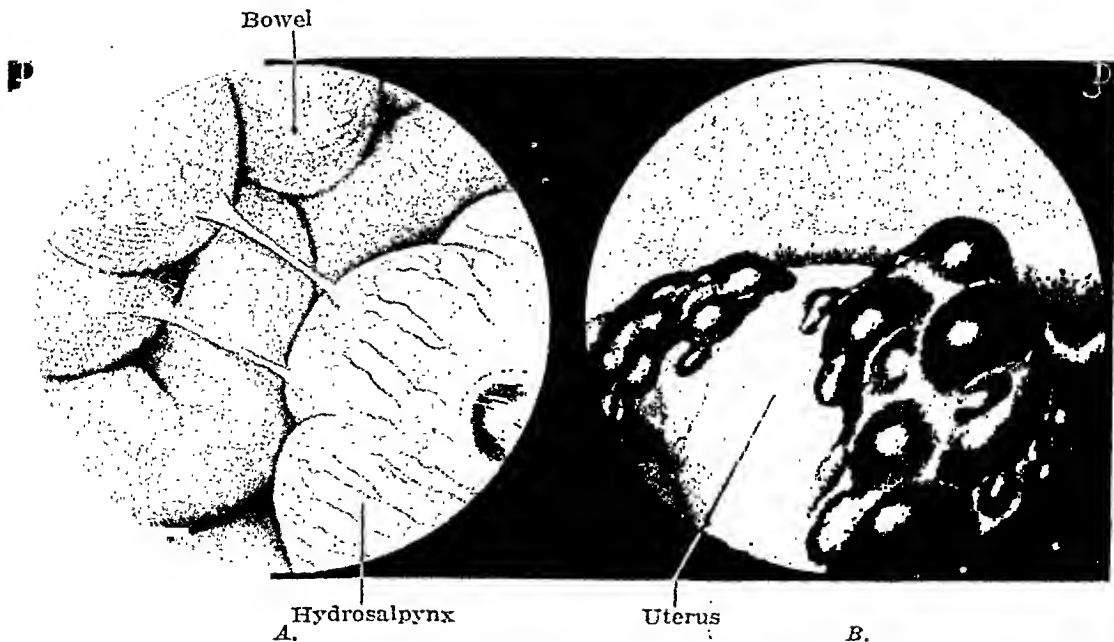


Fig. 10.—A. Culdoscopic view of hydrosalpinx. B. Blood clot on posterior surface of uterus in case of ruptured tubal pregnancy.

hesions. In only a few other cases was it only partially successful because of adnexal adhesions.

In one of the two unsuccessful cases in which the uterus was adherent in the cul-de-sac a peculiar accident occurred. Apparently the trochar passed no further than the subperitoneal space. Air spontaneously entered this space and apparently was trapped there. The next day subcutaneous emphysema was noted over the upper trunk. This persisted to some degree for four days. No harm resulted, and the patient was not uncomfortable. Fig. 13 shows a flat x-ray plate of the abdomen with retroperitoneal emphysema. In two other cases we neglected to force the air out of the abdomen and the patients were moderately uncomfortable for a few days. Fluoroscopy and x-ray plates showed considerable air in the upper abdomen (Fig. 14).

We have had no instances of hemorrhage, peritonitis, or injury to a viscus. Decker reports one case of injury to the rectum with the trochar. The rectal opening was not closed, and the patient recovered without temperature elevation or discomfort.

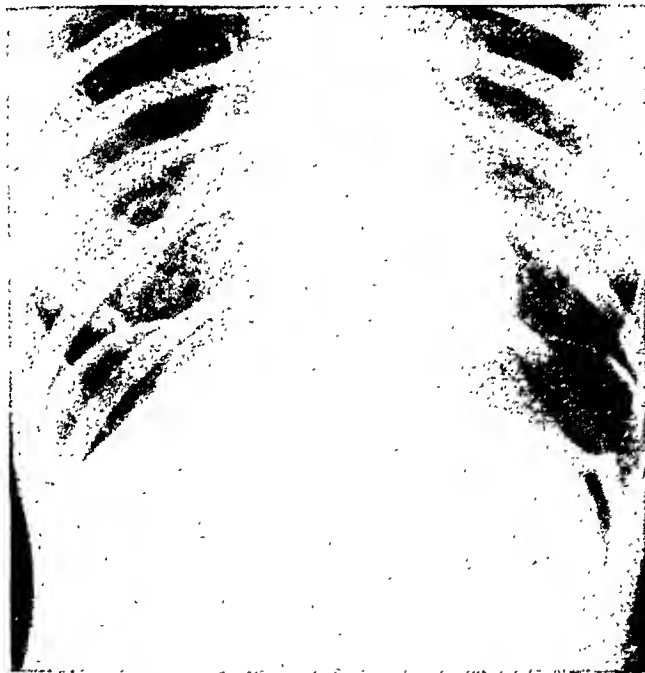


Fig. 14.—Note subdiaphragmatic collection of air twenty-four hours after culdoscopy and failure to force out air from the peritoneal cavity.

Conclusions

Our experience in this series of fifty-six cases in which culdoscopic examination was done brings us to the conclusion that it is a valuable adjunct to the more usual gynecologic procedures. Our prediction is that it will be used eventually with increasing frequency in most clinics. I am reminded of the words of the late Rubin Peterson when in the early days of radiograph studies of the pelvic organs he said, "After some thirty years of experience, I took it for granted that there was very little to be felt in the pelvis that I could not

and the likelihood of opening them by plastic surgery. Also the role of the ovary in sterility can be evaluated by observing follicles and corpora lutea as well as the presence and character of peri-ovarian adhesions. Our present attitude is one of conservatism in its use in sterility cases, but, at any rate, it is one more method available to us of gaining fairly accurate data in selected cases of infertility.

Figs. 8 to 12 show culdoscopic views of various lesions which we have encountered.



Fig. 13.—Shows flat plate of abdomen in a patient with retroperitoneal emphysema.

Contraindications, Failures, and Accidents.—The chief contraindication which we have found to culdосcopy is the presence of a fixed mass in the cul-de-sac. Occasionally a much contracted senile vagina will not permit a satisfactory puncture of the posterior vaginal vault. Also vaginitis contraindicates the entering of the cul-de-sac. A very ill patient, especially one with cardiac decompensation, had best not be put in the knee-chest position but the indication for culdосcopy in such a case would be extremely rare.

Culdосcopy was totally unsatisfactory in two of the fifty-six cases of this series because of a fixed mass in the cul-de-sac. In the light of our present experience no attempt would be made to culdосcope a patient with such a condition. In one other case it was totally unsatisfactory because of cul-de-sac ad-

From the literature and from my colleagues I have the impression that direct study of the pelvic viscera, either by roentgenograph or any other method except open surgery, is sadly neglected, and so I speak on behalf not only of Dr. TeLinde's addition but also on behalf of pelvic roentgenography, either transuterine or transabdominal—a device which definitely adds something to our diagnostic acumen.

DR. TELINDE (Closing).—I believe there are two reasons why Dr. Decker's culdoscope has not been generally accepted. One is that we are all lazy and it is so easy to make a midline incision and see what is in the pelvis; it is a little more difficult to get the patient in the knee-chest position and make the diagnosis by culdoscropy. Another reason is the fear of puncturing a viscus. We have never punctured a viscus. Decker punctured the rectum on one occasion. He simply withdrew the trochar and the patient had no elevation of temperature or other disturbance.

feel. Now, however, I must confess that after my experience with pelvic roentgenology, my eyes have been opened to the fact that there are possibilities in relation to preoperative diagnosis that I never dreamed of." A statement such as that would seem to be justified regarding the direct visualization of the pelvic organs by culdoscopy.

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Discussion

DR. JOHN ROCK, Brookline, Mass.—I have applied this method in 87 patients. I have not been as deft nor as accurate as Dr. TeLinde, because I have failed to enter the cul-de-sac in fifteen cases, that is, one in six. I found that many of the early failures were due to the fact that the point of the obturator had become bent, it merely pushing the peritoneum ahead of it and the alveolar space was entered.

I also made the mistake at first of attempting to enter the cul-de-sac a little too near the cervix. In one patient I am pretty sure that there was just too much fat between the peritoneum and the epithelium, and I attempted to use local anesthesia. I did not realize that the epithelium is so closely approximated to the peritoneum, and that one cannot infiltrate the pelvic cavity.

If the patient does not require general anesthesia, I try to divert her mind and do not use even local anesthesia. Strangely enough, there is comparatively little pain to it. I used carbon dioxide for the first thirty or forty cases. I used pressure to put it in, and that sometimes infiltrates the tissue with gas. I have found now that the use of air is satisfactory, and, with care, pressing on the abdomen and the flanks, the air can be pressed out and the patient made comfortable. The patients have gone home usually on the same day of the examination. Of those who went home promptly, only two or three complained of real distress. Many had shoulder pains such as after insufflation.

I did suture several of the early patients. Most of my cases were sterility patients in whom I could not find any explanation for the sterility. All methods of examination seemed to indicate normality, and yet there had been three or four years of mating. I suspected something to be wrong in the pelvis. I found adhesions involving the right tube fifteen times, the left tube fifteen times, and adhesions of the ovaries three times. These findings were confirmed at subsequent examination in 27 of 28 cases. I examined one patient who gave a history suggestive of ectopic pregnancy and found a large cyst of the ovary. At examination one patient was found to have a solid tumor lying close to the uterus on the left side. She was in the menopause and did not want an operation.

Culdoscopy is a very useful bit of technique in surgery and, as far as I can tell, is comparatively harmless.

DR. JOSEPH L. BAER, Chicago, Ill.—At Michael Reese Hospital, we have concentrated on pelvic roentgenography for over one-fourth of a century. I venture to say that the collection of slides which has been accumulated by Dr. Irving Stein, of our hospital, is perhaps the very best collection of pictures of the pelvic viscera, obtained either by transuterine or trans-abdominal methods, which is extant in this country. We have found this method useful in confirming diagnoses. I believe this method proposed by Dr. TeLinde is one that should be investigated by anyone who is using pelvic roentgenography.

General Considerations

From a clinical point of view it is important to consider the abundant network of nerve endings in the papillae of the dermis. Meissner's corpuscles, end bulbs, and genital corpuscles are plentiful beneath the skin of the labia minora and clitoris. Pressure receptors, the Paccinian corpuscles, are found in abundance in the connective tissue structures of the labia majora and clitoris. The small capillary loops supplying the skin occupy an area in the papillae of the corium in close proximity to nerve endings. It seems reasonable that any internal condition which gives rise to destruction of, or edema around, the small blood vessels would cause considerable irritation of the nerve endings.



Fig. 1.—Edema of the vulva associated with severe toxemia of pregnancy. Asymmetric enlargement of labia was due to a straddle injury in which the vulva struck the side of a bathtub. Vulval edema did not interfere with the spontaneous birth of an infant weighing 2,700 Gm.

In the human subject there are no cyclic changes in the epithelium of the vulva similar to those found in structures of Müllerian duct origin. With regard to changes of the external genital structures associated with puberty, pregnancy, and the climacteric period, there is no variation in the response of the skin of the vulva from that covering other surface areas of the body. The areolae and surrounding skin of the breasts react to endocrine influences in a manner quite parallel to the vulva. While these endocrine influences do cause changes in the secretory appendages of the epidermis, the greatest amount of hypertrophy, and therefore involution, associated with growth and regression is in the underlying

REACTIONS OF THE VULVA TO SYSTEMIC DISEASES*

JOHN PARKS, M.D., AND SHIRLEY MARTIN, M.D., WASHINGTON, D. C.

(From the Departments of Obstetrics and Gynecology of the George Washington University School of Medicine and the Gallinger Municipal Hospital)

UNCERTAINTY surrounding the etiology and management of a number of nonvenereal lesions affecting the vulva caused the present study to be initiated. As investigation progressed it became more apparent that the skin of the vulva represents an area of body surface which readily responds to many internal diseases. Since the gynecologist is often consulted concerning lesions of this area, an understanding of reactions of the vulva to systemic diseases is of real clinical importance.

Through the writings of such authors as Jones¹ and Taussig,² the external genitals of the female have come to be known as the vulva, meaning those structures external to the hymenal ring. Through common usage vulval anatomy now includes the vestibule, urinary meatus, clitoris, labia minora, mons veneris, labia majora, Bartholin's glands, and the perineum.

The vulva develops from outgrowths of mesenchyme covered with ectoderm.³ These ectodermal tissues have characteristic features. The labia minora and clitoris are normally covered with a soft, pliable, stratified epithelium containing sebaceous glands, but no hair follicles and few, if any, sweat glands. The skin of the mons veneris, labia majora, and perineum characteristically has a well-developed horny epithelium, a profusion of hair follicles, sebaceous glands, and many large and small coil sweat glands.⁴ Like other excretory skin structures, the compound racemose Bartholin glands with their columnar epithelium, fibrous capsule, and thin, clear, alkaline secretion are subject to systemic stimuli.

The corium or dermis of the vulva is made up of collagenic connective and elastic tissue of varying thickness, containing an abundance of nerve fibers, blood and lymph vessels, hair follicles, and glands. The cutaneous vessels supply the skin with products for regeneration, nutrition, and growth. They carry away many of the products of skin metabolism. A dense network of small blood vessels spreads out as a very complete sheet in the most superficial part of the corium parallel to the outer skin surface. These minute terminal arterioles and capillary loops represent the major area of metabolic exchange in the skin.⁵

Since the epithelium contains no blood vessels, its nourishment is received through lymphatic exchange in the intracellular spaces. Pathologic manifestations from systemic diseases are usually first seen in the underlying corium where the capillary loops are in contact with the basal cell layer of the epithelium. Skin changes from internal disease occur from within outward.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

Dermatologic lesions always warrant careful evaluation. At the turn of this century Fox expressed an opinion regarding dermatology which is particularly applicable to diseases of the vulval epithelium. He stated that a name alone for a pathologic condition is not enough, but that an accurate appreciation of the conditions which are present both in the skin and in the internal organs, as well as the various causes which tend to produce these conditions, should be determined in each instance.⁶

At examination it is well to remember that common skin lesions such as lichen planus, allergic reactions, herpetiform infections, psoriasis, and other dermatologic conditions which cause changes in the epithelium may be greatly distorted in the vulva due to secondary infection and ulceration. In every patient with vulval disease the gynecologist should not only inspect the vulva but look elsewhere for skin lesions. The lips, mouth, tongue, hair line, axillae, palms of the hands, back, and breasts are particularly important areas for investigation. Signs of infections should be looked for in the urethra, Bartholin glands, vagina, and cervix.



Fig. 3.—Ulceration of the vulva in aplastic anemia.

In all instances of vulval ulceration, minimal laboratory studies should include a complete blood count; urine examination, particularly for sugar and acetone; cultures for gonococci and mycotic organisms; and a hanging drop examination for *Trichomonas vaginalis*. Indications for biopsy, venereal disease tests, and special blood chemistry studies should be determined by the history and characteristics of the lesion.

Blood Dyscrasia

Agranulocytosis, aplastic anemia, and acute leucemia cause peripheral vascular changes which result in deep, punched-out, oval areas of vulval ulceration

tissues which are of mesodermal origin. Considering the epidermis of the vulva as tissue quite comparable to other surface coverings of the body such as the breasts and lips, it seems probable that the subepithelial structures and the location of this area in relation to the organs of excretion are more important than the inherent characteristics of the epithelium itself.

Frequent trauma, constant contamination, warmth, and moisture increase the metabolic demands of the surface epithelium of the vulva. Where these conditions prevail, skin resistance to systemic disease is decreased.

The large amount of subcutaneous areolar tissue, the folds of easily distended epithelium, and the large number of blood and lymph vessels permit tremendous edema of this area. Edema frequently accompanies and probably contributes a great deal to the itching associated with such conditions as toxemia of pregnancy, urticaria, herpes zoster, the early forms of atrophic dermatitis, and many other skin conditions which involve the vulva.

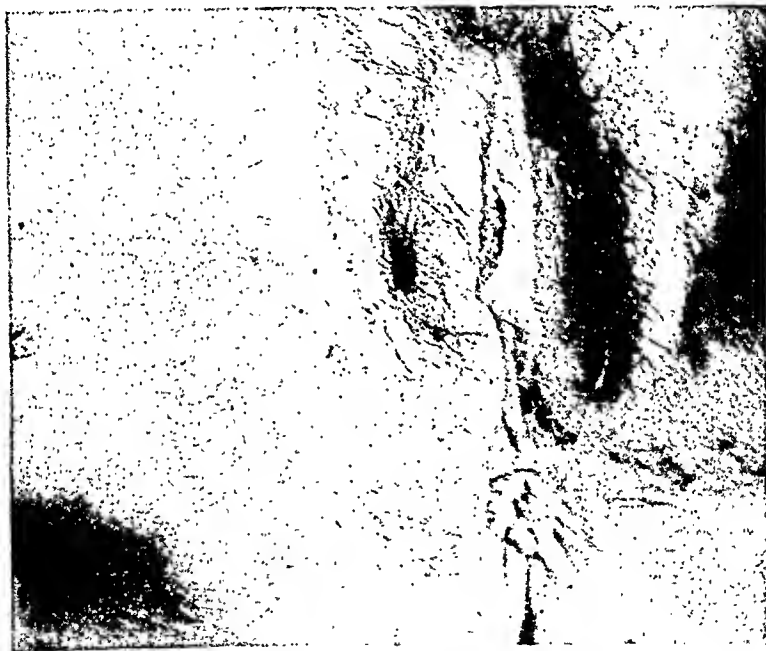


Fig. 2.—Psoriasis of the vulva, thighs, and perianal area. Lesions on the vulva were distorted by irregular lichenification and ulceration.

In trying to arrive at a diagnosis of a noninfectious vulval lesion, there are a few important points in history taking which may be outlined as follows: (1) The duration of the condition. (2) The character of symptoms, particularly with reference to the degree of itching and edema. (3) The exact site of origin of the complaint (this frequently is best obtained by having the patient point directly to the area of initial involvement). (4) History of dermatologic reactions to common substances such as soaps, ointments, medications, disinfectants, douching materials, and clothing. (5) History of menstrual function. (6) Diurnal variation of symptoms. External irritants are usually noticed during the day. Epithelial irritations of internal origin often become more intense at night.

The Vulva in Uremia

A typical ulceration of the vulval epithelium occurs in patients with slowly developing uremia. In gynecology, uremia is most frequently seen complicating carcinoma of the cervix. Weight loss, tissue dehydration, and avitaminosis contribute to the typical vulva changes seen in uremia. The inner surfaces of the labia minora and the most dependent parts of the labia majora show a superficial excoriative type of ulceration, covered with a thin, grayish membrane and surrounded by brownish encrusted crystals of urea and uric acid. In the case of a patient with carcinoma of the cervix and bilateral pyelonephritis, the blood urea nitrogen was 75 mg. per cent. Following treatment of her pyelonephritis and avitaminosis, the blood urea nitrogen returned to 15 mg. per cent and the vulva healed.

Diabetes Mellitus

There are several factors in diabetes mellitus which produce circumstances favoring dermatitis of the vulva. Inadequate metabolism of carbohydrates and fats causes disturbances in cellular nutrition. Diabetic patients on a high carbohydrate diet and large doses of insulin frequently show symptoms of B avitaminosis. Great utilization of carbohydrate rapidly exhausts any scant supply of nicotinic acid and riboflavin which the patient may have.⁷ Vitamin deficiency causes edema and itching which results in trauma to the epithelial surfaces of the vulva. Another way in which the diabetic patient develops vulvitis is due, in all probability, to the glucose-containing urine keeping the vulva moist. This is particularly true of the patient with constant dribbling. The sugar-containing urine and sebaceous secretions present on the vulva result in a culture media quite favorable for the growth of fungi and many other bacteria common to this area. Quite frequently intertrigo from obesity contributes to the diabetic patient's vulval dermatitis (Fig. 5).

Treatment of the diabetic patient with vulval infection should be directed first to correction of the diabetes plus adequate supplemental vitamins, particularly those of the B-complex group, and reasonable cleanliness. Various local applications may be used to combat surface infections, depending upon the etiology of the predominating organism. In mycotic vulvovaginitis, good results have been reported with treatment consisting of a nonirritating, nonstaining jelly containing calcium and sodium propionate.⁸ The important principle is not to add an irritating therapeutic agent which will contribute additional trauma to the partially devitalized cutaneous structures. As soon as the systemic condition is corrected, the surface epithelium usually heals quite rapidly.

Vitamin Deficiencies

Probably the most common vitamin deficiency influencing the skin of the vulva is that associated with the B factors. Because the underlying vitamin deficiency is often mild and manifestations in the vulva are soon camouflaged by secondary infections, the basic diagnosis of vitamin B deficiency is frequently missed. A lack of riboflavin favors *Candida* (*Monilia*) infections. Skin ulcerations secondary to pellagra are often infected with Vincent's organisms.⁹ When

covered with a thin, grayish membrane and surrounded by very little induration or redness. An example of this type of ulceration in a patient with aplastic anemia secondary to sulfanilamide poisoning is given in Fig. 3.

This patient had received approximately 15 Gm. of sulfanilamide from her family physician for treatment of a sore throat. When admitted to the hospital, two weeks after receiving the sulfanilamide, she was found to have ulcerative lesions of the oropharynx similar to those found on the vulva and in the vagina, as well as retinal hemorrhages and bleeding from the gum margins. Her hemoglobin was 35 per cent; red blood count was 1,280,000, and the white blood count was 1,040, with 96 per cent lymphocytes and 4 per cent neutrophils. Prior to death her white blood count went down to 770 per cubic millimeter, all of the cells being monocytes. Bleeding time was twelve and one-half minutes. Prothrombin time was 57 per cent of normal. Blood platelet count varied from 48,000 to 27,300 per cubic millimeter.



Fig. 4.—Ulceration and hyperpigmentation of the vulva in pernicious anemia.

Pernicious anemia is a deficiency disease which gives rise to tissue devitalization. The sensitive epithelium of the vulva readily reflects the avitaminosis and disturbed metabolism associated with pernicious anemia. Vulval lesions in a patient with an acute exacerbation of pernicious anemia are shown in Fig. 4. This patient's hemoglobin was 20 per cent; red blood count was 670,000, and the white blood count was 2,050. Gastric analysis showed no free hydrochloric acid. Blood urea nitrogen was 19 mg. per cent. Areas of ulceration with secondary surface infection were found in the bladder mucosa, tongue, and mouth, as well as on the vulva. With treatment consisting of blood transfusions, liver extract, thiamin chloride, nicotinic acid, and cevitamic acid, all of the surface ulcers promptly healed.

B deficiency, they may cause the appearance of lesions characteristic of thiamin, nicotinic acid, and riboflavin deficiency. Metabolism of estrogens increases the demand for vitamin B.

Many years before there was much discussion about vitamin metabolism, Fox recognized that "all therapeutic agencies which equalize the circulation, strengthen the digestive functions, induce refreshing sleep, and improve nutrition of the body will be found to be powerful factors in the cure of cutaneous disease."¹⁶ In addition to the rather typical lesions of riboflavin and nicotinic acid deficiency, a number of other conditions which frequently involve the skin of the vulva have been attributed to various vitamin inadequacies. There has been a recent tendency to assign specific vitamins to certain skin diseases. For example, patients with eczema have been reported to respond to pyridoxine;¹³



Fig. 6.—Chronic atrophic dermatitis of the vulva.

psoriasis has been treated successfully with vitamin D;¹⁴ lichen planus has cleared up under treatment with vitamin B complex;^{15, 16} and of particular importance to the gynecologist have been studies indicating the possible influence of vitamin A deficiency in the development of chronic dermatitis of the vulva with kraurosis and leucoplakia.^{17, 18}

The clinical significance of achlorhydria, a finding rather common to women past 50 years of age, in relation to skin changes in the vulva is not very clearly understood. It is known that gastric achlorhydria prevents the extraction of vitamins from their natural sources in food.⁷ Patients with longstanding vitamin A deficiency frequently show gastric hypoacidity.¹⁹ Thiamin and nicotinic acid are essential to the normal function of the gastroenteric tract.²⁰ However, in evaluating gastric acidity, the many factors influencing gastric secretion such as emotional status, reverse peristalsis, and salivary secretions must be considered along with the nutritional state of the patient. Mitra and Varma found no significant correlation between gastric acidity and the orogenital syndrome of

either of these infections is found in patients with pregnancy, diabetes, alcoholism, hyperthyroidism, fever, or any debilitating condition, vitamin B deficiency must be considered as a predisposing factor in the infection.

Vitamin B factors are essential in the continuous process of cellular nutrition and respiration. Sydenstricker indicates that thiamine, nicotinic acid, and riboflavin function partly as activators in carbohydrate dehydrogenation and are constantly regenerated. They also are components of coenzymes which are used up and require constant replacement. Disturbance in cellular function is due to the coenzyme action of these vitamins. Neurons are the cells most sensitive to the oxygen want association with early nutritional deficiency.⁷ This may be a factor in hypersensitivity and itching of the vulva before edema and changes in the epidermis are evident.

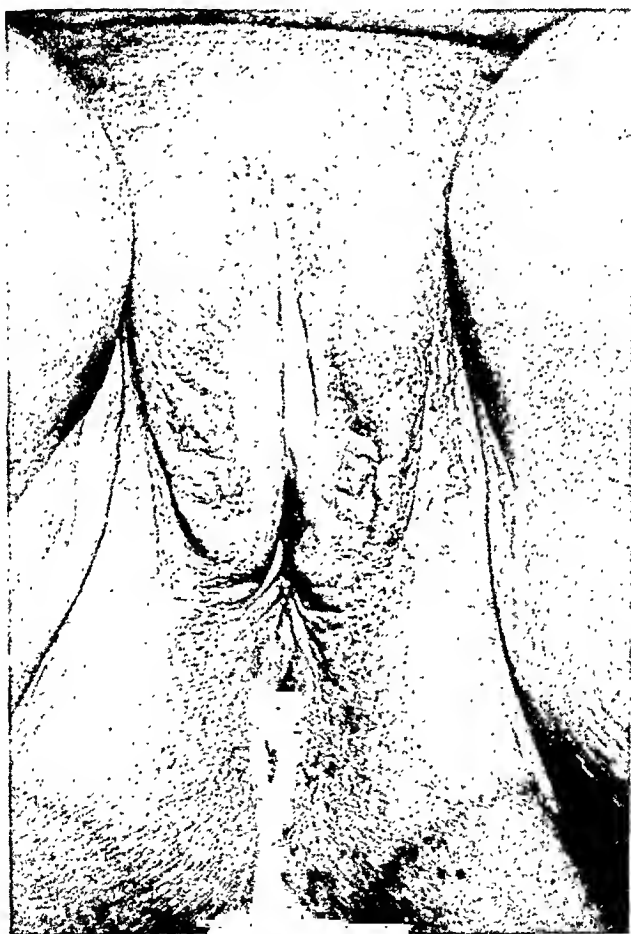


Fig. 5.—Dermatitis in a diabetic patient with urinary incontinence and intertrigo.

Bean, Spies, and Vilter have demonstrated that asymmetric skin lesions can be produced in a susceptible pellagrin without exposure to sunlight by any mechanism which prevents a blood supply sufficient in amount to satisfy the local tissue demands. Where local anoxia and increased metabolism prevail as in sores, pressure, irritation, friction, or inflammation, local lesions may occur.¹⁰

Increased metabolism and unknown factors associated with pregnancy disturb the normal vitamin requirements. The pregnant and lactating patient needs three times the thiamin supply of the nonpregnant patient.¹¹

According to Ashworth and Sutton,¹² estrogens do not aid in the utilization of the vitamin B components. When given to patients with subclinical vitamin

Characteristic changes in the epithelium involve all cell layers. Atrophic changes, ulceration, and hyperkeratosis are so frequently found in a relatively small section of the vulva that it is difficult to distinguish distinct epithelial phases of the disease (Fig. 8). In normal metabolism the basal cells are the only epithelial structures which can reproduce. In atrophic dermatitis, the basal cell layer is distorted and frequently shows more than a normal number of mitotic figures. Hydropic changes in the basal and prickly cells are a common finding (Fig. 9). These two cell layers represent that portion of the epithelium in which there is a circulation of lymph. The outer three layers of the epithelium contain no lymph supply. In association with hyperkeratosis, the granular layer next to the prickly cells contains many granules of eleidin. The cause of hyperkeratosis is unknown. Cellular anoxia and friction stand out as significant possible factors in the excessive keratinization seen in leucoplakic dermatitis. Increased deposition of eleidin and keratin in the skin of older people is not limited to the vulva. These changes are often seen on the backs of the hands, over the knees and elbows, and about the mouth. The anatomic characteristics of the vulva and its close relationship to the excretory orifices contribute to the severity of keratotic skin changes in this part of the body.

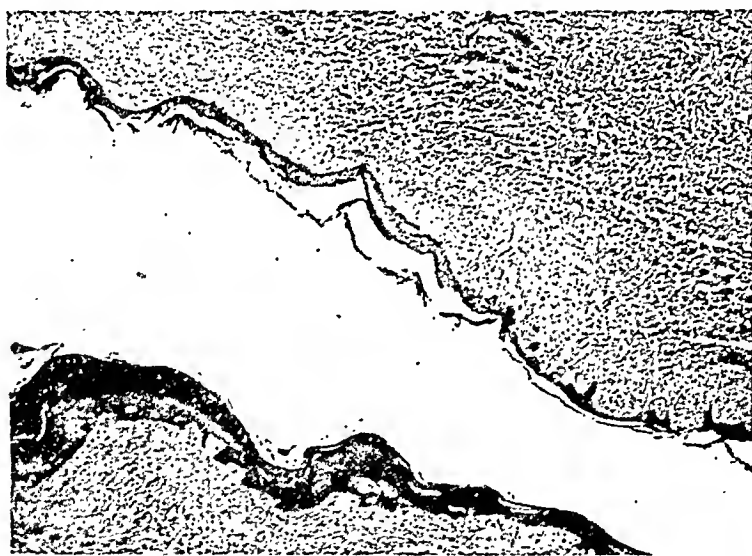


Fig. 8.—Atrophic dermatitis and hyperkeratosis in adjacent areas of the vulva.

Primary and secondary changes seem to occur in the dermis. Capillary dilatation and subepithelial edema disturb nerve endings, giving rise to itching. External trauma from scratching introduces bacteria into the subepithelial tissues. Healing of minute areas of ulceration is accompanied by the deposition of a homogeneous collagenous tissue which takes a connective tissue stain. Elastic fibers are reduced in number. Round cells infiltrate the dermis and extend into the germinal layers of the epithelium. Thus far, there is no clinical evidence that the collagenous scar tissue in the superficial portion of the dermis can be resolved by any type of therapy. This layer of avascular tissue deprives the

vitamin deficiency.²¹ The administration of dilute hydrochloric acid in therapeutic doses fails to raise the free acidity in the stomach during digestion of a regular meal. The spectacular therapeutic results sometimes obtained with dilute hydrochloric acid administration remain unexplained. Most foodstuffs have a neutralizing influence on hydrochloric acid.²² Additional investigation is needed to clarify the relation of achlorhydria and vitamins in skin changes of the vulva.

Chronic Atrophic Dermatitis of the Vulva

The terms "chronic atrophic dermatitis of the vulva," "leucoplakic vulvitis," and "kraurosis vulvae" are used interchangeably to designate a clinical syndrome in which the tissues of the vulva undergo a low grade inflammatory reaction with associated atrophic and hypertrophic changes in the corium and epithelium. Detailed clinical and pathologic changes which characterize this disease have been described in excellent articles by Taussig,² Graves and Smith,²³ Counsellor,²⁴ Usher and Campbell,²⁵ Adair, Davis, and Schuitema,²⁶ Brewer,²⁷ and Savill.²⁸



Fig. 7.—Section of chronic atrophic dermatitis of the vulva showing marked hyperkeratosis, acanthosis, distortion of the basal cell layer, vascular dilatation, hyalinization of the dermis, and round cell infiltration.

A brief discussion of chronic atrophic dermatitis is included in this presentation to emphasize the internal factors which may contribute to its etiology. While the cause of this disease remains unknown, neurogenic, hormonal, nutritional deficiency, and allergic theories imply a subepithelial beginning for the atrophic and hypertrophic changes which characterize the condition.

Current studies seem to indicate that the primary histopathologic change in chronic atrophic dermatitis of the vulva involves the papillae of the corium and the basal cells of the epidermis (Fig. 7). This is the vital metabolic zone of the skin. Any disturbance in this zone will be reflected in the epithelium and in the underlying mesodermal tissues.

Allergic Dermatitis

Many women, particularly those of the older age group, show varying degrees of sensitivity to drugs, soaps, and clothing which come in contact with the skin of the vulva. It is difficult to say what part achlorhydria, deficient diets, and antibody formations have to do with these reactions. Frequently the skin of the vulva is not the only area showing localized sensitization. Some of the more common contributors to this type of localized dermatitis are: phenolphthalein, impure soaps, rectal ointments, phenol-containing douching materials, and underclothing. Poorly processed rayon and garments with incompletely fixed dyes are particularly common causes of vulvitis. Pure cotton or wood cellulose used in making rayon should cause no allergic reaction. However, synthetic resins, sulfonated oils, and formaldehyde preparations used to process or finish rayon may become important sensitizing agents which give rise to localized dermatitis.³²

As observed on the vulva, the first reaction to localized allergic dermatitis is edema and itching followed by secondary trauma from scratching. The labia become swollen. The sebaceous glands of the labia minora stand out in relief. There is puckering about the hair follicles of the labia majora as a result of subcutaneous edema. Fissures form over the perineal body and in the labial folds.

In arriving at a diagnosis, a careful history is essential. Because the patient has a localized sensitization to an unconcentrated irritant, patch tests are usually unsatisfactory. Two patients illustrate these points.

CASE 1.—One month following repair of a complete procidentia, a white patient 60 years of age returned for postoperative examination with a newly acquired extensive dermatitis of the vulva. Tense, shiny, thin epithelium covered the edematous labia. Lateral to the labia majora there was an increased amount of pigmentation. Linear fissures were present in the labial folds posteriorly. She had noticed a controllable amount of itching of the vulva. Her hands were healing from a slight rash which she thought resulted from the use of a cheap, highly scented soap. Examination showed no evidence of anemia, avitaminosis, or glycosuria. Stilbestrol ointment and a diet high in vitamin B failed to produce any remarkable improvement in the patient's vulval condition. On closer questioning it was found that her particular vulval reaction had come about while wearing certain newly acquired undergarments. As a clinical trial, all local treatment was stopped and the patient was asked to wear the rayon clothing in contact with the vulva day and night for one week. The intensity of the vulvitis increased immensely (Fig. 10). Thereafter, the only treatment advised was a change to cotton underclothing. Within a period of four weeks the vulva had healed completely. Three months later the patient gave herself another clinical trial with rayon. Her symptoms returned, but rapidly subsided as soon as the rayon no longer came in contact with the vulva.

CASE 2.—Another example of vulval sensitivity was that of a nurse, aged 53 years, who had had itching in the region of the labia and perineum for a period of six months. The itching became worse during the day and was especially noticeable by evening. She had been using an antiseptic powder containing carbolic acid in a douche. Her history included a marked reaction to some rayon and wool undershirts which had been packed in a moth preventative. She had been on a diet low in protein and roughage due to a gastrointestinal

skin appendages of nutrition. Hair follicles, sebaceous glands, and sweat glands undergo atrophy. The epithelial surface may be edematous, glistening, red, wrinkled, retracted, white, or thickened, depending upon the degree of edema and scarring of the dermis, and upon the severity of surface infection secondary to external trauma.

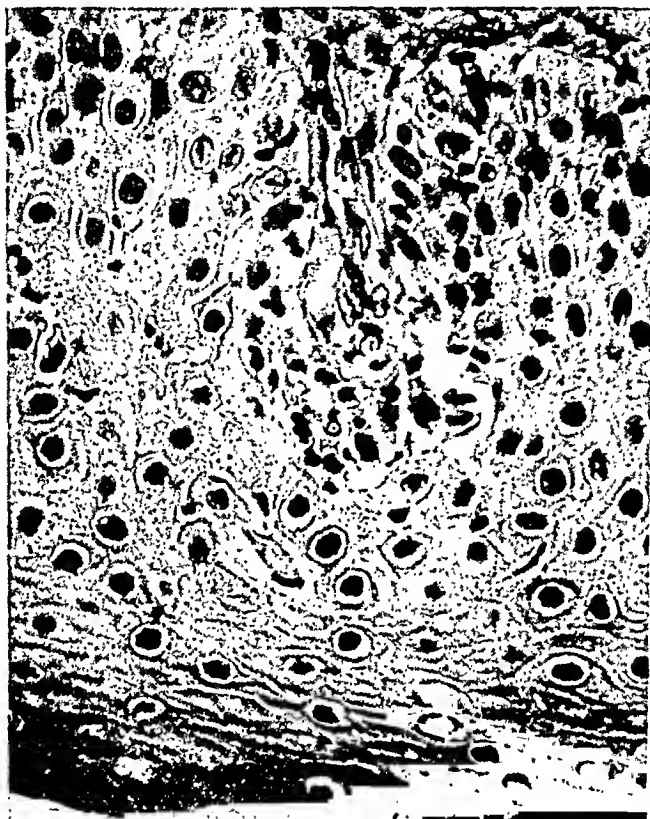


Fig. 9.—Section showing mitotic figures and hydropic degeneration of the basal and prickle cell layers in chronic atrophic dermatitis.

Treatment of atrophic dermatitis of the vulva has been directed at measures which reduce inflammation, alleviate pain, improve cell metabolism, and remove permanently damaged tissues. Eradication of all foci of infection is strongly advised. Nerve resection is recommended in selected circumstances.^{24, 25} At present, medical treatment with vitamins and estrogens frequently improves the skin condition of patients with atrophic changes of the vulva, but these forms of therapy should be used only in the early stages of the disease and under the most careful clinical control.^{17, 18, 29, 30, 31} Estrogen ointment applied locally produces as effective results in the epidermis of the vulva as oral administration of the drug. Local application carries with it none of the stimulating influences to the uterus and ovaries which are seen with the use of intramuscular or oral estrogens.

In the present state of our knowledge, where scarring causes symptomatic constriction of the vulva or where the vulva shows areas of ulceration and marked hyperkeratosis, the involved tissues should be removed by wide excision.

chronic atrophic dermatitis, certain common dermatologic conditions, and allergic reactions have been described and illustrated with colored slides.

The authors wish to express their thanks to Ann Browning Snodgrass, Technician in Neurology, for the special preparation and staining of slides used in this presentation; and to Victor R. Landi, Medical Photographer, for the photomicrography.

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Discussion

DR. JEAN PAUL PRATT, Detroit, Michigan.—Skin lesions of the vulva present interesting problems for diagnosis and treatment. Dr. Parks has selected a number of excellent characteristic illustrations. He has also presented a sound anatomic basis explaining the lesions.

I should like to describe a few cases to illustrate a group of metabolic disturbances which show evidence of hyperthyroidism and a lowered threshold for sugar.

The first is a girl 16 years of age who complained of itching and discharge. She was slightly overweight for her height and age, but generally healthy. We found this typical change of the skin of the vulva which shows a metabolic disturbance and, in addition, scratch lesions which became infected. The scratch lesions responded to anti-septic treatment promptly, but the skin lesion remaining was found to be largely due to hyperthyroidism. Her basal metabolism rate was minus 10, sugar tolerance normal. She tolerated 2 grains of thyroid, but her trouble was not relieved until carbohydrates in her diet were reduced. Control was difficult, as she was away from home at school most of

condition which had been diagnosed as visceroptosis and spastic colitis. Medical examinations had shown achlorhydria. Significant findings were localized to areas where she had come in contact with synthetic materials. There was a linear ulceration behind her left ear immediately beneath the plastic material covering the framework of her glasses. Her external genitals showed oval, raised areas of superficial ulceration taking on an irregular pattern over the most prominent portions of the somewhat edematous labia and perineum. There was no inflammation around the anal orifice. The patient's vulval lesions and the ulceration behind her left ear cleared up within three weeks after the plastic guard was removed from her glasses and after she changed to a nonirritating type of undergarment.



Fig. 10.—Allergic dermatitis of the vulva resulting from sensitivity to rayon.

Summary

Regional reactions of the vulva to a number of noninfectious systemic diseases may be explained by anatomic and metabolic factors peculiar to this area of the body surface. Because of its vascularity, abundant nerve supply, frequent trauma, constant contamination, warmth, moisture, and variable histologic structure, the vulva frequently reflects deficiency diseases, metabolic disorders, and allergic reactions. The gynecologist is often consulted concerning lesions of this area which are, in reality, indications of internal disease. Some clinical points in identification of vulval lesions associated with such diseases as diabetes mellitus, pernicious anemia, aplastic anemia, uremia, vitamin deficiency,

abnormal, of so many and varied orifices. These discharges are modified not only by local disorders but also by diseases of remote organs and tissues. Their effect may be either direct or indirect.

We are confronted with a variety of local manifestations which are the result not only of regional factors, but may also arise from hereditary and environmental conditions independently or concomitantly with other dermatologic disorders.

Formerly, we at the University of Chicago did some work on a condition known by various names which we described as chronic atrophic dermatitis. We felt that fundamentally it was an atrophic condition of the dermis which affected the vessels, nerves, and tissues of the corium. It was our opinion then that, when the itching and irritation could not be relieved, excision was the best procedure not only to relieve symptoms but also to reduce the real threat of the development of carcinoma.

If the measures suggested by Dr. Parks or new means of alleviation arise in the future, the indications for removal might cease to exist.

In conclusion, I should like to stress again the ideas presented by the author that one should not be satisfied with a diagnosis of a local disease necessarily of local origin, but should evaluate all local and general factors which could be responsible for the regional manifestations. The diagnosis should be based upon the status of the patient and not be limited to the condition of the vulva.

DR. PARKS (Closing).—A point has been brought up which I should like to emphasize, and that is the use of stilbestrol in the treatment of vulval disease. For skin lesions, local application seems just as effective as systemic administration, and the patient experiences none of the uterine changes associated with its general use. In addition, stilbestrol seems to influence vitamin B metabolism. Skin lesions of patients with vitamin B deficiency may be aggravated by the use of stilbestrol.

the year. Her intelligence permitted satisfactory management of her therapy by herself, particularly after the benefit to be derived from treatment was demonstrated to her. So long as she adheres strictly to the prescribed treatment she remains symptom-free and local evidence of metabolic disturbance disappears.

Another girl 10 years of age complained of itching. The change in the vulva which was also very suggestive of a metabolic disturbance was found. Her basal metabolic rate was minus 2; glucose tolerance was normal. She tolerated only one-fourth grain of thyroid. A low carbohydrate diet was advised. Treatment was carried out by her pediatrician, who informed us that more than one-fourth grain of thyroid produced symptoms of asthma. In a month she was improved but not relieved of itching. After eighteen months the character of the lesion had changed and was then typical of psoriasis, though she had not complained of any other lesion on the body and none were found. Here we were mistaken in our diagnosis. This patient's lesions looked like those of the first patient, but this proved to be a local psoriasis.

A third patient, a woman of about 55 years, complained of intensive itching and a vaginal discharge. The itching was the major problem, and the lesion suggested atrophic dermatitis. She had some evidence of metabolic disturbance and was treated with a low carbohydrate, high protein diet. She experienced some relief, but the lesion improved only up to a certain point. She remained so disturbed that she was only relieved by a vulvectomy.

A similar patient about 55 years of age was disturbed with itching. She was rather obese, had a normal basal metabolism, and a normal sugar tolerance. We have learned by experience, however, that the laboratory tests do not always make a correct diagnosis, and that therapeutic tests are often more valuable.

We reduced the carbohydrates in her diet. She tolerated about a grain of thyroid. This patient loved to eat and thought the treatment was hardly worth while and returned to her sweets. She returned feeling that the treatment was of very little use, but after three trials she was convinced that the cure lay within her own hands. As long as she continued the treatment we advised she remained symptom-free.

Another patient showed an atrophic vulvitis with ulceration. We saw her only once and found the symptoms rather characteristic of a metabolic disturbance in connection with the atrophic vulvitis. She was given thyroid to tolerance, a low carbohydrate diet, and stilbestrol. Her physician reported that she was entirely well six months later. We were suspicious that the ulcer might be malignant and we were relieved to learn that the ulcer had healed.

The patients just presented demonstrate the value of therapeutic tests when laboratory tests are negative. A normal basal metabolic rate and normal sugar tolerance do not exclude the possibility of metabolic changes in the skin of the vulva.

DR. FRED L. ADAIR, Chesterton, Indiana.—In discussing the excellent presentation, one is inclined to re-emphasize the fact that the obstetrician and gynecologist must never neglect to consider that he is dealing with an individual woman and not with an anatomic and physiologic set of organs or their parts: and that these structures are subject to disorders which may be of local origin or the local reaction be due to a more general condition which has a major local reaction.

There are some points of local interest which should be stressed. The vulva is the most complicated of the dermatologic structures of the human body with its hair follicles and sebaceous and sudoriparous glands; its various types of epithelia and modified glandular structures. It is also complicated with numerous folds and pockets which are in contrast to the more generally smooth dermal structures of the rest of the body.

One can also postulate that this area not only responds to the growth, development, age changes, and abnormal manifestations of other skin structure, but that it participates in the changes which occur in the sex organs at the onset of the menopause, also in those which occur as the result of pregnancy, parturition, and the puerperium. It is also worthy of note that no region of the human body is exposed to the effects of the discharges, normal and

The diagnoses of condyloma and leucoplakia scarcely need further comment. They were recognized grossly and were symptomless, except that bleeding occurred in one patient with condylomata, and in another there was a profuse leucorrhea. Both instances of leucoplakia merely showed whitish plaques on the cervix which histologically were composed of markedly thickened squamous epithelium. The basal cells showed no abnormal changes suggestive of a "pre-cancerous" or cancerous condition.

The Normal Cervix During Pregnancy

An enormous number of papers and monographs dealing with the gross and histologic changes in the cervix uteri during pregnancy has accumulated over a period of more than a century. For instance, in a monograph published in 1897, von Franqué¹ cited 210 references, and many articles have appeared since that time. These studies, however, have been concerned mostly with the formation of the lower uterine segment or with cervical dilatation during labor, and the generally accepted description of the cervix during gestation is that presented by Stieve² in his classic paper which appeared in 1927.

According to Stieve, there is during the premenstruum an enlargement and increased secretion of the cells of the cervical glands which he considered a preliminary to the transformation which occurs during gestation. In the first two and one-half months, however, the most prominent changes are to be found mainly in the connective tissue elements. The cervix is composed mostly of fibrous tissue, and the individual cells increase in size and multiply in number. The muscle plays a secondary role, as recently emphasized by Danforth,³ but its cells also hypertrophy and reach their maximum by about the third month. The most striking finding at this early stage is a tremendous increase in the number of blood vessels and lymphatics, and this continues throughout the whole of pregnancy, so that eventually the cervix becomes a soft boggy structure comparable to "erectile tissue." There is a considerable invasion of the mucosa with leucocytes, wandering cells, and plasma cells, but Stieve failed to find any clear evidence of decidua formation. The occurrence of islands of decidualike cells, however, were described by von Franqué,¹ Ulesco-Stroganoff,⁴ and others.

During early pregnancy there is an increased activity of the cervical glands. The individual cells increase in height, proliferate, and there is a marked production of mucus. This change is progressive throughout pregnancy, but does not become striking until after the twelfth week. From then on the glands increase in number, invade the substance of the cervix, and project into the cervical canal. The average depth of the glands in the nonpregnant cervix is from 1 to 2 mm., but during gestation they measure from 4 to 6 millimeters. The result of this proliferation means a marked increase in the radial measurement of the cervix, half of which is now composed of mucosa. The extension of the glands into the cervical lumen throws the mucosa into manifold folds which form the *arbor vitae*. It has a very distinct honeycomblike appearance, with numerous projections into the cervical canal. These changes, if accepted as the normal picture, are of especial importance in interpreting the significance of the so-called cervical erosion of pregnancy (Figs. 1 and 2).

A CLINICAL AND HISTOPATHOLOGIC STUDY OF LESIONS OF THE CERVIX UTERI DURING PREGNANCY*

C. F. FLUHMANN, M.D., SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine.)

AN IMPORTANT feature of prenatal care is a careful inspection of the cervix uteri. This procedure often reveals pathologic lesions which exist with or without symptoms such as vaginal bleeding and demand immediate attention. The object of this study is to present an analysis of the histopathologic findings in a series of 89 cases where a gross abnormality was recognized, and a biopsy of the cervix obtained, or a hysterectomy performed.

Material

This study is based on the examination of tissue obtained from the cervix uteri of 89 patients at various stages of gestation. Pedunculated growths such as cervical and endometrial polypi had been removed by twisting off with a pair of forceps or a snare, and were available in toto for examination. The recognition grossly of carcinoma, condyloma, and leucoplakia called for a biopsy from the site of the lesion. In the group listed under "erosion of the cervix" the diagnosis in twenty-eight cases was based on biopsy specimens which had been obtained because the observer considered the appearance of the cervix as suspicious of a possible malignancy. In four instances a total hysterectomy had been performed because of a mistaken diagnosis, and all occurred before 1930, that is, before facilities for the routine performance of endocrine pregnancy tests had become available. The clinical description of these four cases mentioned the existence of a cervical erosion. Two cases, one with a cervical erosion and another with carcinoma, were ectopic gestations. Of the eighty-nine cases, forty were private patients under the care of various members of the staff, while forty-nine were from the clinic.

All stages of gestation are represented. Sixteen specimens were taken during the second month, twenty-six during the third, twelve during the fourth, seven during the fifth, twelve during the sixth, six during the seventh, six during the eighth, three during the ninth, and one at term. A survey of the age groups shows a fairly even distribution between 18 and 41 years, except for the cancer patients where the majority fell in the late thirties (Table II).

The histopathologic diagnosis showed the following distribution:

Cervical polypi	37
So-called erosion	32
Carcinoma	10
Condyloma acuminata	5
Endometrial polypi	3
Leucoplakia	2
Total	89

*Presented at the Seventieth Annual Meeting of the American Gynecological Society, June 17 to 19, 1947, Seignior Club, Montebello, Quebec.

So-Called Cervical Erosion During Pregnancy

Most textbooks of obstetrics make a reference to the frequent occurrence of erosions, especially in multiparas, but fail to offer much more information. In order to obtain some data as to their occurrence, a series of 119 consecutive private patients was analyzed. It is seen from Table I that at the first prenatal visit an erosion was observed in fifty-seven, or 48 per cent, of all groups. There was little difference between primigravidae and multigravidae, since an erosion was found in thirty-seven of seventy-one of the former and in twenty of forty-eight of the latter. If not significant, it is at least of interest that a definite difference was observed between the patients seen early in pregnancy and those who reported for their initial visit in the later months. Of fifty-one first seen during the first twelve weeks seventeen, or 33 per cent, had a cervical erosion while thirty-four, or 66 per cent, did not, while of sixty-eight seen in subsequent months forty, or 59 per cent, had an erosion and in twenty-eight, or 41 per cent, none was demonstrable. Since the effect of labor as a causative factor in the production of erosions is not known, a comparison of findings during the prenatal period and at postpartum examination are not of much value. Nevertheless, of seventy-nine patients seen both before and after delivery forty-four, or 55 per cent, had an erosion during the course of gestation while 65, or 82 per cent, presented this lesion when seen six to eight weeks post partum.

TABLE I. INCIDENCE OF SO-CALLED CERVICAL EROSIONS AT FIRST PRENATAL VISIT IN A SERIES OF 119 PRIVATE PATIENTS

MONTH OF PREGNANCY	GRAVIDA I		GRAVIDA II OR MORE		TOTAL	
	EROSION	NO EROSION	EROSION	NO EROSION	EROSION	NO EROSION
2	11	22	6	12	17	34
3	10	6	5	5	15	11
4	3	0	1	7	4	7
5	6	2	3	0	9	2
6	2	1	1	3	3	4
7	2	0	3	0	5	0
8	3	3	1	0	4	3
9	0	0	0	1	0	1
Total	37	34	20	28	57	62

The gross appearance of a cervical erosion during pregnancy is familiar to all of you. It is essentially a very shallow ulcer with fairly clear-cut edges. Its size varies greatly for it may be a circular lesion one to 2 cm. in depth about the external os or it may occupy only a small segment or again it may extend far up on the portio vaginalis. The base may be smooth or have a granular appearance, and when there is a concomitant infection varying numbers of Nabothian follicles stand out as small yellow points. Its flaming red color is very characteristic, and is especially pronounced when the vaginal mucosa assumes the deep purplish hue so characteristic of pregnancy. It usually bleeds readily on the slightest manipulation.

A diagnosis of erosion of the cervix was made in thirty-two patients of this series, and it was based both on the clinical features of the gross lesion and on

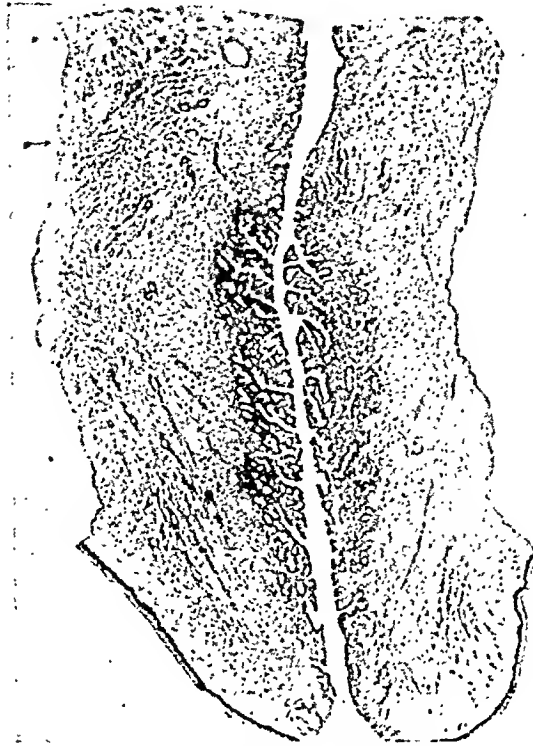


Fig. 1.—Longitudinal cross section of normal nonpregnant cervix uteri. After Stieve.²

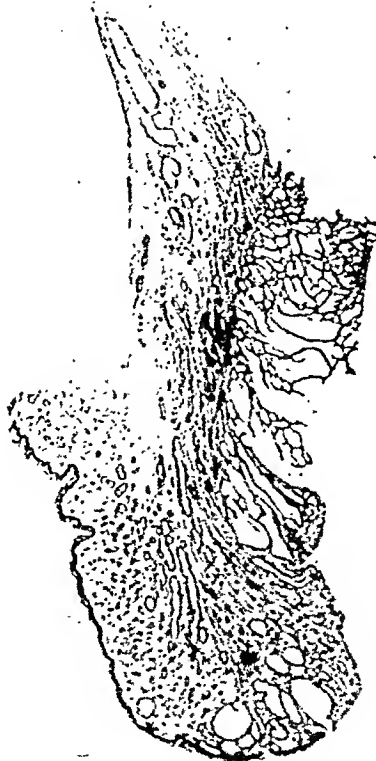


Fig. 2.—Longitudinal cross section of cervix uteri during eighth month of gestation. After Stieve.²

the histopathologic examination. In 19 cases there were no associated symptoms, and the erosion was discovered on routine examination. Frank bleeding, usually of spontaneous origin, was mentioned in six cases, while "spotting" or a blood-tinged discharge occurred five times, and in two instances the patients complained of an unduly profuse white discharge.

The histologic examination showed a wide variety of changes at the sites of the erosions and they may be considered under separate headings: (a) adenomatous proliferation of the glands, (b) papillary outgrowths, (c) edema and increased vascularity, (d) infiltration with inflammatory cells, (e) epidermidization, hyperactive basal cells and hypertrophy of squamous epithelium, and (f) formation of decidua.

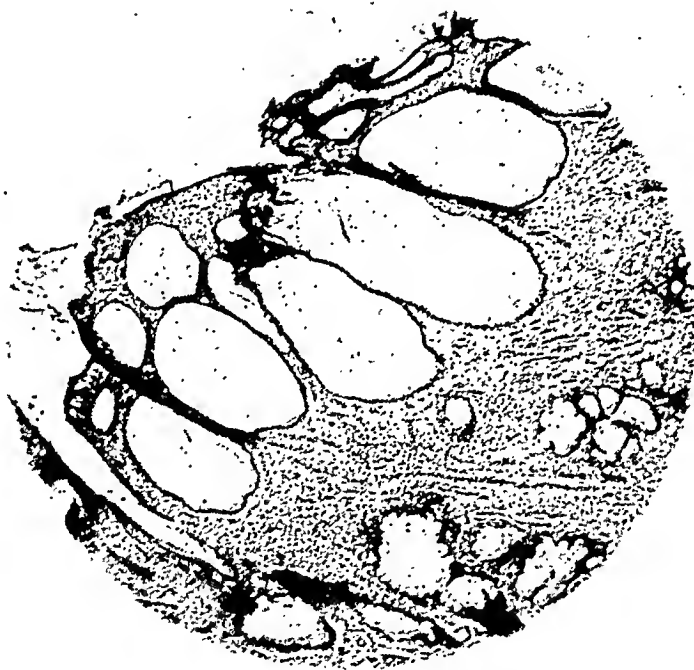


Fig. 5.—Adenomatous proliferation with many cystic glands are a characteristic finding in cervical erosions during gestation.

(a) *Adenomatous proliferation of the glands* is the most striking change observed in cervical erosions during pregnancy and is probably the basic structure of this lesion. The lining cells are of a very high cylindrical type (Fig. 3) and increase to such an extent that often they become stratified and form small projections into the lumina of the glands (Fig. 4). The glands themselves increase greatly in number, and interspersed among those with this type of epithelium may be found many distended cystic structures with the lining cells of the low cuboidal variety. These glandular formations are not only seen at the surface but extend into the substance of the cervix and may reach a depth of as much as 6 to 8 mm. (Figs. 5, 6, 7). The covering epithelium is invariably of the high cylindrical cell type but it may also alternate with patches of squamous epithelium.

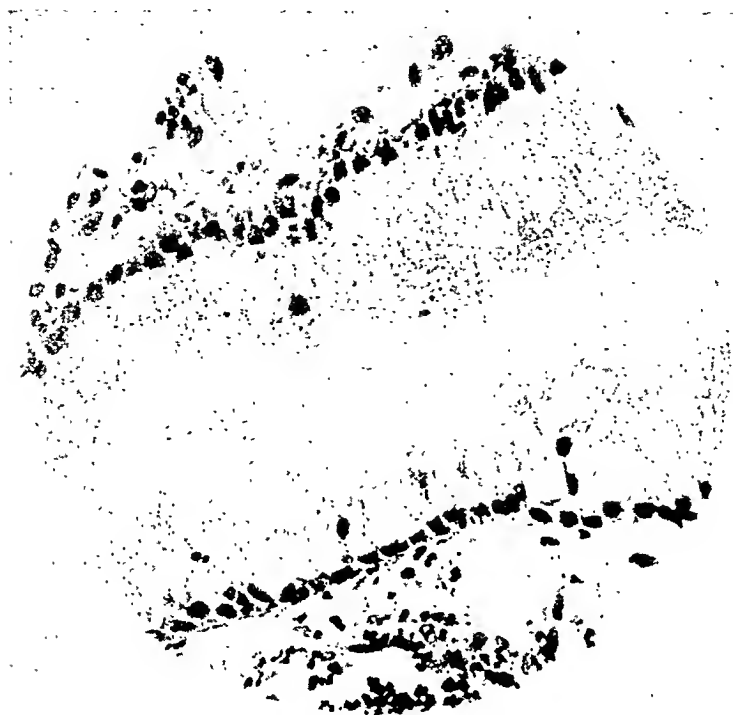


Fig. 3.—Characteristic high cylindrical epithelial cells lining cervical glands during gestation.

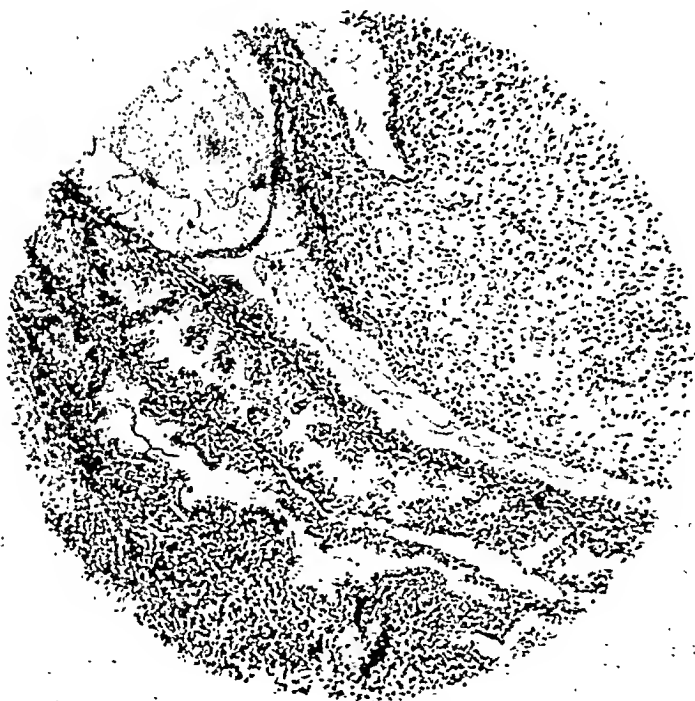


Fig. 4.—Active proliferation of cells lining cervical glands during pregnancy result in stratification, and there are small projections into the lumina. This photomicrograph shows decidual reaction of the stroma on the right.

This adenomatous process was demonstrable in twenty-four of the thirty-two specimens. Among these an intense cervicitis only occurred five times and a moderate infiltration with leucocytes, plasma cells and histiocytes occurred in seven. The marked glandular process was accompanied by papillary outgrowths, as described below, in ten instances. There was a hypertrophy of the squamous epithelium twice, and six times there was either a hyperactivity of the basal cells or epidermidization. In six cases islands of decidua-like cells were noted, and in one instance this change was widespread throughout the whole microscopic section.

In two biopsies no glandular elements were seen. Of these, there was an extensive cervicitis in one, moderate round cell infiltration in one, hypertrophied squamous epithelium in one, and islands of decidua in two.

(b) The second characteristic feature involving the cylindrical epithelium was an extensive *papillary outgrowth* such as occurs in "papillary" or "granular" erosions in the nonpregnant (Figs. 8, 9). These formations are generally attributed to a hyperplasia of the connective tissue which lies between the various glands.

There were six instances of the thirty-two where these papillary proliferations were the predominant feature. An extensive cervicitis was present in three, moderate round cell infiltration in four, hypertrophied squamous epithelium once, and in three, islands of decidua were observed.

(c) *Edema and increased vascularity* were particularly in evidence in all instances.

(d) *Infiltration with inflammatory cells* is of especial importance because of the prevalent concept, advanced by Robert Meyer⁵ and others, that all erosions should be considered as the result of an infection. However, a marked cervicitis could be demonstrated in only nine of the thirty-two cases with erosion; in twelve there was a moderate infiltration (usually in limited areas) with leucocytes, plasma cells and histiocytes; while in eleven such wandering cells were only of rare occurrence. This observation is certainly contradictory to Stieve,² who reported this change as a constant finding in the normal cervix during pregnancy.

(e) *The occurrence of a hyperactivity of the basal cell layers of the squamous epithelium and of epidermidization* are of especial importance in view of the search for methods dealing with the recognition of early carcinomatous changes. These abnormal proliferations are especially prone to occur during pregnancy and consequently, there is here a wide field for further investigation and observation. The subject has been discussed many times in the past, for example by Meyer,⁵ Fluhmann,⁶ Novak,⁷ and recently Te Linde and Galvin⁸ again focussed attention on this subject in a paper presented before this Society.

Of the thirty-two patients of this series with erosion of the cervix, an excessive hypertrophy of normal squamous epithelium was seen four times, while epidermidization or hyperactive basal cells appeared in six instances. All of the latter were in the group characterized by an adenomatous proliferation of the glands.

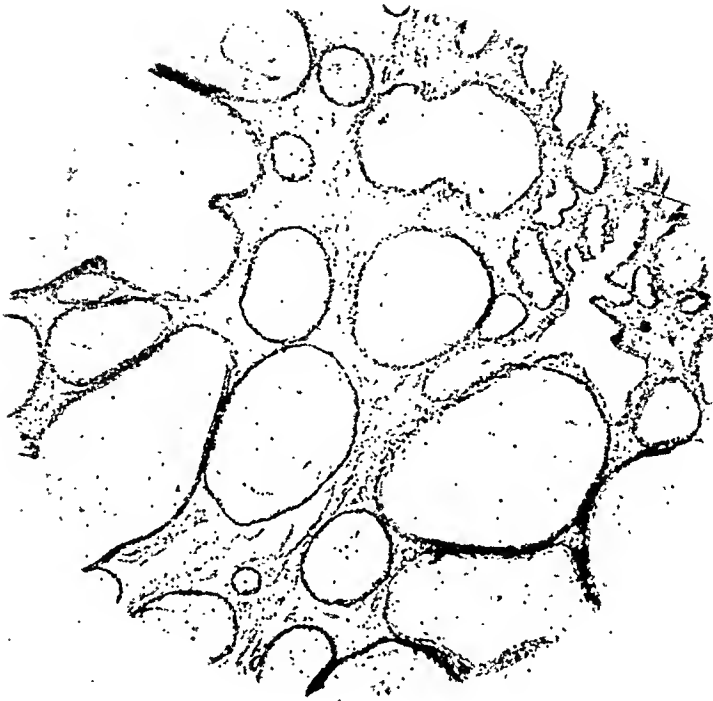


Fig. 6.—Cystic glands in adenomatous proliferation accompanying cervical erosion during pregnancy.

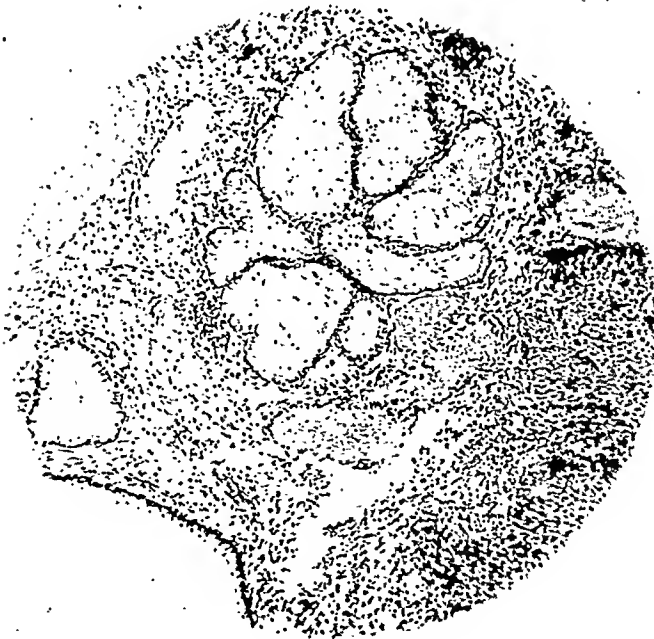


Fig. 7.—Adenomatous change in erosion with basal cell hyperactivity of surface squamous epithelium on the right.

When "epidermidization" or "epidermidalization" occurs the cylindrical epithelium is found undermined by developing basal cells. These proliferate, become stratified, undergo vacuolation, and gradually displace the cells at the surface. The individual cells, however, stain evenly, do not show undue variations in size, and mitoses are infrequent (Fig. 10). In the case of basal-cell hyperactivity, an already fully developed squamous epithelium sends out shoots or branches containing immature rapidly proliferating cells which stain irregularly. There may be considerable variation in the size of the individual cells, and many mitotic figures can be found (Figs. 11, 12). It is this picture which presents a difficult problem in differentiation from an early carcinoma. These two processes are thus very distinct entities, but both frequently may be observed in the same specimen.

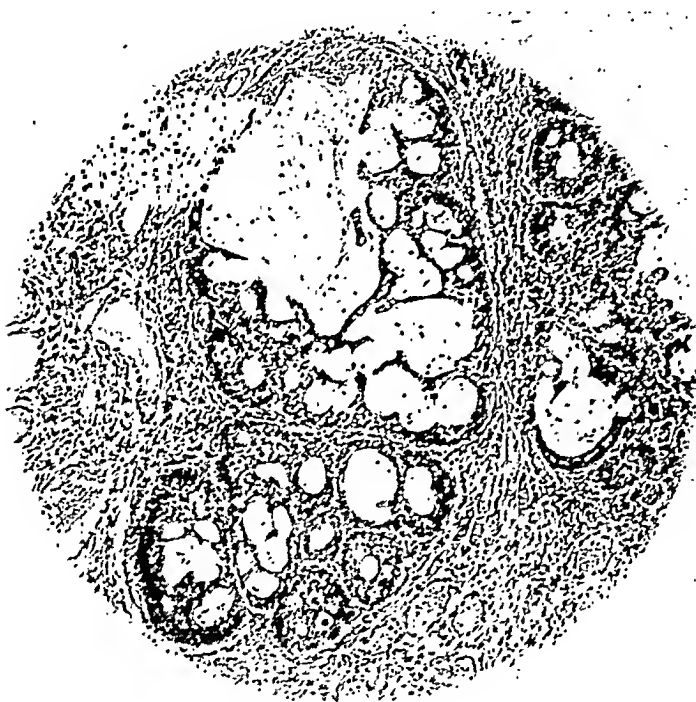


Fig. 10.—Epidermidization of glandular epithelium in cervical erosion during pregnancy.

(f) *Formation of decidua.* Although Stieve² failed to demonstrate the presence of decidua in the pregnant cervix, it has been described by von Franqué,¹ Ulesco-Stroganoff,⁴ and numerous others. In this study an extensive transformation of the stroma into decidua was noted only once, but isolated islands of this tissue occurred in eleven instances. It was generally found near the surface and also in some of the papillary outgrowths (Fig. 9), and, although the cells unmistakably were decidual in nature, they were not as fully developed as those seen in the endometrium.

Etiology of Cervical Erosions During Pregnancy

An analysis of the observations recorded in the preceding section leads to the suggestion that, although some probably result from an inflammatory con-



Fig. 8.—Papillary outgrowth in cervical erosion during pregnancy.



Fig. 9.—Papillary proliferation in cervical erosion during pregnancy with marked decidual reaction in one projection at upper center.

dition which may have existed before the pregnancy, most of the cervical erosions seen during the course of gestation are not the result of a cervicitis, but are a type of adenoma. There is thus an extension of proliferating glands either from the cervical canal or from glands which normally open on to the squamous epithelium of the portio vaginalis.

The evidence advanced is not conclusive, but certain points are worthy of emphasis. (1) In a small series, half the patients had a cervical erosion at some time during pregnancy, a proportion much too great for the normal female population. (2) Only one-third of the patients seen during the first twelve weeks had an erosion, but after this time 59 per cent did have. This observation suggests that erosions appear at about the same time that the maximal normal proliferation of the cervical mucosa occurs. (3) The histologic examination of 32 erosions, all of which (with the exception of the four hysterectomies) were extensive enough to warrant obtaining a biopsy specimen, showed the existence of an extensive cervicitis in only nine instances.

Mucous Polyps of the Cervix Uteri

As might have been predicted, the largest group of the series was of mucous polyps originating either from the external os or from the cervical canal. There were specimens from thirty-seven patients, and their gross appearance and characteristics are so well-known that it is superfluous to enter into any details at this point. It might be mentioned, however, that bleeding occurred only in six instances.

The histologic examination presented a series of pictures which closely resembled those described under "erosions of the cervix," but there were a few notable exceptions. Extensive inflammatory processes were more frequent, and occurred in seventeen of the thirty-seven cases, while a moderate infiltration with round cells was observed six times. The formation of decidua was much more marked and even involved the whole polyp in twelve, while isolated islands of deciduallike tissue were seen three times. Epidermidization and hyperactivity of basal squamous epithelial cells were noted in six cases. Fig. 13 illustrates one of the serious problems resulting from this finding. The surface epithelium was either of the cylindrical or squamous type, or both were present at various levels. It is possible that some of these polyps may have been of endometrial origin.

The basic structure of the polyps on histologic examination showed that they could be grouped into four categories according to the behavior of the cylindrical cell epithelium.

1. In thirteen instances the polyp was essentially an adenoma with marked proliferation of glands, many of which were dilated and cystic.

2. Ten were mostly papillary offshoots such as described in the section on cervical erosions.

3. A moderate proliferation of the glandular elements, in fact, scarcely more than one would expect in a normal cervix, was noted seven times.



Fig. 11.—Hyperactive basal cell epithelium in erosion during gestation.

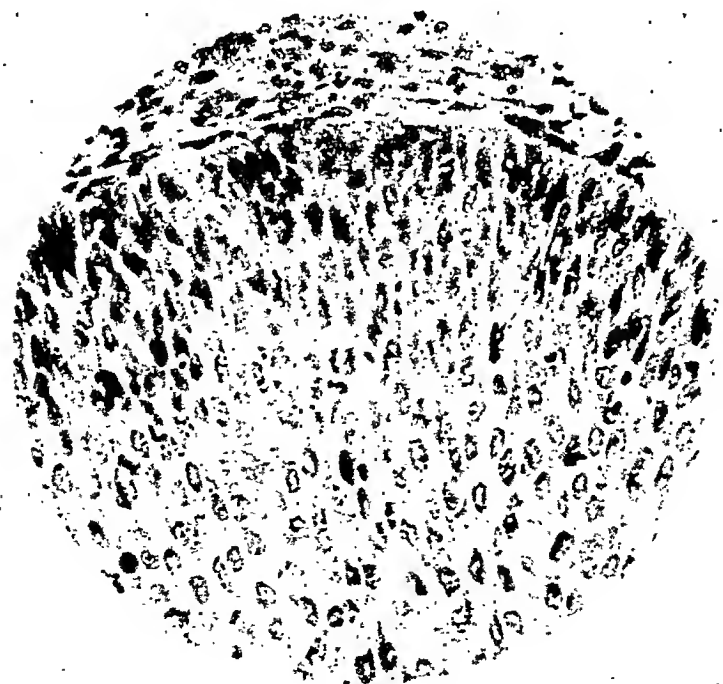


Fig. 12.—High power view of hyperactive basal cells in cervical erosion during pregnancy.

TABLE II. STANFORD SERIES OF CERVICAL CARCINOMAS ASSOCIATED WITH PREGNANCY

NO.	LAB. NO.	AGE	GRAVIDA	PARA	MONTHS PREGNANT	TYPE CARCINOMA	DEGREE MALIGNANCY	CLINICAL CLASSIFICATION	TREATMENT	RESULT
1	5177	25	iii	ii	2	Squamous	Immature	Inoperable	Radium	Died end of fourth year
2	A3918	32	vi	v	7	Squamous	Immature	Border	Radium x-ray	Alive 5 years later
3	3292	38	v	iv	4	Adenocarcinoma	Mature	Operable	Hysterectomy	Alive 6 years later
4	A3496	36	iii	ii	4	Adenocarcinoma	Mature	Border	Hysterectomy	Died 7 years later
5	A3565	37	i	i	Term	Squamous	Midmature	Operable	Radium	Alive nineteen years later
6	A4962	38	i	0	3	Squamous	Immature	Operable	Radium	Died 9 years later
7	RS431	26	iv	ii	6½	Squamous	Immature	Operable	Radium hysterectomy	Alive 6 years later
8	C6118	36	ii	ii	3	Squamous	Mature	Operable	Radium	Died gas bacillus infection during treatment
9	C6593	27	i	0	2	Squamous	Mature	Operable	X-ray radium laparotomy for ectopic	Alive 6 months later
10	C6825	36	v	iv	6	Squamous	Midmature	Operable	Hysterotomy radium	Under treatment May, 1947

4. In seven cases no glands were seen in the sections studied. These polyps were composed mostly of a core of connective tissue and some muscle cells, with a surface epithelium. Extensive decidual formation was demonstrable in six, a marked inflammatory reaction in five, and several showed areas of necrosis.

Endometrial Polyps

Three polyps with their base high in the cervical canal have been classified as endometrial in character and doubtless arose from the isthmus of the uterus. The two criteria on which this diagnosis was based were (a) the fact that they were composed almost entirely of decidual and the individual cells, as compared to the usual cervical polyps, were larger and stained more regularly and deeply, and (b) the few glands present were not of the cervical type but resembled glands from the isthmus in their usual incomplete stage of secretion.

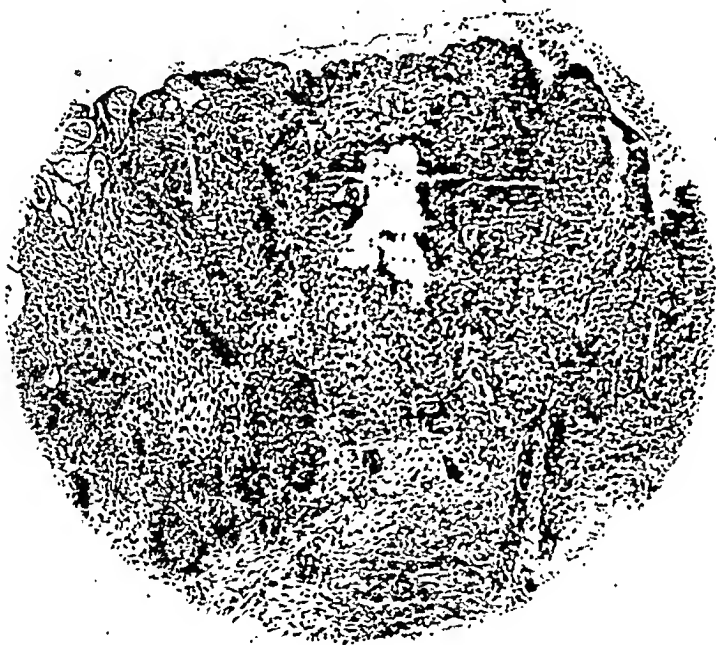


Fig. 13.—Hyperactive basal cells from a cervical polyp removed during early pregnancy. Three observers considered this lesion as of a carcinomatous nature, but some doubt was entertained and a subsequent biopsy of the cervix from the region of the base of the polyp did not show any malignant change. The patient was allowed to continue to term and had a normal delivery and postpartum course. Four years later there is no demonstrable lesion of the cervix. (Private patient of Dr. Frank Norris.)

Carcinoma Cervicis Uteri

The subject of cancer of the cervix uteri during pregnancy is far beyond the limits of this paper, but because of its very nature some mention must be included. In 1934, Emge⁹ presented before this Society a report on six cases of cervical cancer in pregnancy which had been observed at Stanford. Some details are given in Table II and, of the six, one had died after four years and two were known to be alive five and six years later. No further information

Discussion

DR WALTER T. DANNREUTHER, New York City.—We have all seen pathologic lesions of the cervix from time to time in pregnant women, but perhaps have failed to realize that there was much difference in their character from similar lesions encountered in the non-pregnant. It would be interesting to know how high an incidence the 89 cases reported by Dr. Fluhmann represents. Since 40 were private patients, the percentage obviously cannot be calculated, but perhaps Dr. Fluhmann can tell us the total number of obstetrical patients in the clinic among whom the remaining 49 cases were found.

It is not surprising that cervical polypi and erosions constitute a little more than 75 per cent of all the pathologic conditions discovered, because these occur so frequently in young women. And since there is increased physiological activity, hyperemia, hypertrophy and endocervical glandular stimulation during pregnancy, it is natural that pre-existing lesions should be involved in these alterations.

Dr. Fluhmann found 57 erosions in 199, or about 50 per cent, of his own private patients. Sometimes these erosions are so massive that the gross appearance closely resembles carcinoma. I have seen two such cases with a shaggy, extensively papillomatous surface which bled easily, and both showed the same adenomatous changes mentioned by Dr. Fluhmann. Incidentally, both patients miscarried in the sixth month. I agree with the essayist that all cervical erosions do not show evidence of infection and endocervicitis, and that decidual reaction of the stroma cells is not a constant finding.

Cervical carcinoma occurring in the pregnant uterus presents a serious clinical problem, and each case confronts us with an individual therapeutic question. However, it seems logical always to regard the carcinoma as of major importance.

DR. T. K. BROWN, St. Louis, Mo.—Dr. Fluhmann has emphasized the importance of careful inspection of the cervix in prenatal care. He has gone further than this and obtained the histopathologic findings in a series of 89 such cases. Most of us would probably have made similar observations and have treated the abnormality by some simple procedure such as cauterization, coagulation, or evulsion. The author went further than this and obtained biopsy specimens when indicated by suspicious areas.

Analysis of the diagnoses in this series revealed ten cases of carcinoma of the cervix. Four cases have been diagnosed since 1934. On the service at Washington University, Hobbs has reported four cases of carcinoma during pregnancy in a similar period of time.

The changes in the cervix during pregnancy described by Stieve, Danforth, and Schwarz indicate that there is hypertrophy of the cells and increase in the number of blood vessels and lymphatics. The proliferation of the glandular structures of the cervix during pregnancy is also marked. It seems that this increase in bulk of the tissues in this area can account for the development of cervical erosion during pregnancy by simple eversion of this excess tissue through the external os. These changes persist in varying degrees into the puerperium.

Another pathologic condition which may be encountered during pregnancy is endometrial implants on the cervix and vaginal mucous membranes. These areas may bleed and present an appearance very similar to carcinoma of the cervix.

I should like to ask the essayist how his plan of treatment of cases with carcinoma of the cervix associated with pregnancy varies according to the stage of pregnancy at which the patient is first observed.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Fluhmann has presented us with an interesting study on a subject concerning which our knowledge has been very incomplete. While it might be expected that the cervical mucosa, being a Müllerian derivative, is under the hormonal control of the ovarian hormones, I know of only one really worth-while study of its cyclical histology, that of Sjövall of Stockholm.

Again, since the vaginal mucosa is so responsive to hormonal, more particularly estrogenic, influence, why should this not apply also to the squamous epithelium of the pars vaginalis, which is its direct continuation? And why may not such an estrogenic stimulus explain some of the milder instances of "basal cell hyperactivity," which I personally feel

could be obtained on these, but of the other three, one died after seven years, one after nine years, and one has survived and is in good health after nineteen years.

There are four cases to add to the series, three of which are so recent as to offer little practical information. However, all four were seen early in the course of the disease and were diagnosed as in stage I or "operable." The first (No. 7 in table) had an immature squamous cell carcinoma, was seen at six and one-half months, and has survived six years after treatment with both radium and hysterectomy. The second (No. 8), first seen at six months, was transferred to the County Hospital and tragically died of a gas bacillus infection following the first radium application. The third (No. 9) was recognized six months ago as having an early cancer of the cervix, but shortly after radium therapy had been initiated her complaint of a two months' period of amenorrhea was found to be attributable to an ectopic gestation and a laparotomy for this condition was performed. The fourth (No. 10) is a very recent patient who reported with an early cancer of the cervix and pregnancy at six months. A hysterotomy has been performed and she is now under radium therapy.

Summary

This report is an analysis of eighty-nine specimens obtained from the cervix uteri in a group of women at all stages of gestation. Four were obtained by hysterectomy and the others by removal of a lesion recognized grossly or by a biopsy of the cervix.

Gross and histopathologic examination revealed that mucous polyps of the cervix were found in thirty-seven, erosion of the cervix in thirty-two, carcinoma of the cervix in ten, condyloma acuminata in five, endometrial polyps in three, and leucoplakia in two.

A histopathologic analysis of thirty-two so-called "erosions of the cervix" extensive enough to warrant obtaining a biopsy specimen, suggests that this lesion should be considered as an adenoma of the cervix rather than an inflammatory condition.

As a matter of record, some details are given of the ten cases of carcinoma of the cervix uteri seen during pregnancy in the Department of Obstetrics and Gynecology of the Stanford Medical School.

My thanks are due to Mr. Pierre Lassègues for the photomicrographs, and to Mrs. Joseph S. Rogers for her assistance in the preparation of the manuscript and the clinical follow-up studies.

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tients in other hospitals, it would have been impossible to calculate the total number of obstetric cases from which the specimens were obtained.

I was interested in hearing Dr. Brown speak of endometriosis. We have seen it in the cervix and vaginal wall, but not during pregnancy.

The treatment of cancer during pregnancy is far beyond the limits of this paper. We would certainly treat a cancer early in pregnancy very differently from one near term. The last patient noted in Table II was treated with hysterotomy, followed by irradiation. All the cancer patients listed in Table II were proved cases both clinically and histologically. None could possibly be considered as representing the so-called preinvasive type of lesion.

In no instance did an abortion result from the manipulation incident to obtaining a biopsy of the cervix. However, since it is necessary to cauterize the area from which the specimen is taken and a dirty slough results, the possibility of infection is present especially if an abortion should result. For this reason, no biopsies were performed purely to gratify scientific curiosity, and in all cases the visible lesion was regarded as suspicious.

I cannot tell for certain if any of the biopsies were obtained from the cervical canal in the presence of extensive lacerations, but if so they must have been too few in number to change the general picture described in my paper.

I am in full agreement with Dr. Kosniak and Dr. Martzloff that the term "erosion" is a bad one, but it is in such general usage that any attempt to introduce a new one would probably not be successful. It, of course, refers to the gross appearance of the lesion and, as I have indicated, there are wide variations in the histologic picture.

have been overaccented in the feverish search for the earliest phases of cervical carcinoma? It would seem that this point could be clarified by sufficiently extensive studies of biopsies or surface scrapings of cervixes at various phases of the cycle.

Decidual reaction in the cervix is not a very common finding, but over the years we have seen a considerable group of such cases in our laboratory. As to erosions and polyps, it is of practical clinical importance to remember that vascular lesions of this sort are a not uncommon cause of bleeding during pregnancy. Since many patients interpret almost any vaginal bleeding as menstruation, such lesions are always to be thought of when women report that they "menstruate" even though pregnant.

DR. WILLARD ALLEN, St. Louis, Mo.—I have recently had the privilege of seeing a patient with profound, extreme erosion of the cervix occurring during pregnancy. Two competent gynecologists had already made a provisional diagnosis of carcinoma of the cervix without being aware of the pregnancy. We had to avail ourselves of the rabbit test to be certain of the diagnosis of pregnancy. The lesion was of the cauliflower type of carcinoma of the cervix and measured about 6 cm. in diameter. The only thing that made me suspect that the lesion was probably not malignant was the difficulty encountered in making a satisfactory biopsy.

I want to emphasize the rapidity of the changes in the cervix. This patient was less than two months pregnant when first seen. She aborted spontaneously at about three and one-half months of pregnancy. I saw her three weeks following the abortion. At that time there was no erosion, nothing but a deep laceration extending up to the internal os and thereby exposing the cervical canal so that what we had seen and thought was carcinoma was nothing but the changes of normal pregnancy made visible by the old laceration.

I would like to ask how many of Dr. Fluhmann's patients had deep cervical tears so that he could see far into the cervical canal and not merely into the os?

DR. GEORGE W. KOSMAK, New York City.—I would like to ask if Dr. Fluhmann could find a more suitable and descriptive term for what he calls "erosions." It always offends my editorial sense to see that word used.

DR. KARL MARTZLOFF, Portland, Oregon.—It is embarrassing to be the only one to voice a dissenting note in this otherwise serene discussion, but I could see no anatomic evidence of bona fide cervical erosion in Dr. Fluhmann's sections. The histologic appearance of his material is characteristic of the commonly observed circumstantial vermilion zone. I would therefore like to ask Dr. Fluhmann how he uses the term "erosion." It is rather tragic to see patients possessing a vermilion area about the external os of the cervix, who have been informed that they have an ulcer which needs cauterization or some other form of therapy. This often is the beginning of a course of questionable cervical tinkering to an area which is certainly not an erosion and possessed of no serious pathologic significance. Occasionally, these areas can have their superficial epithelium knocked off by light trauma, and they may then bleed readily.

Did any of Dr. Fluhmann's erosions show actual loss of substance with a fibrinocellular membrane covering the site of the epithelial loss? This, it seems to me, is the minimal requirement for diagnosis of a bona fide benign erosion.

I would also like to ask whether the carcinomas that Dr. Fluhmann observed were well developed so that one might detect them readily by inspection, or did they belong to the so-called noninvasive types of cancer?

It should also be mentioned that polypoid hyperplasia of the mucosa of the cervical canal may occur in the absence of pregnancy. I know of nothing that is more confusing to the naked eye observation of the cervix than this alteration which may grossly resemble cancer but which on histologic examination shows a benign polypoid change.

DR. FLUHMAN (Closing).—I am very sorry that I cannot use these cases from a statistical standpoint as they are merely 89 specimens found at random in the laboratory. Many of them were from private practice, and since many of our men deliver their pa-

CASE 1.—H. D., Hospital No. 52733, was a 33-year-old Negro primigravida admitted to the St. Louis Maternity Hospital on March 1, 1947. Her expected confinement date from the menstrual history was January 14, 1947, but the fetal heart was first definitely heard in November, 1946. Fetal movements were felt by the patient in October, 1946. Beginning two weeks prior to admission, painless uterine contractions were noted and the membranes had ruptured spontaneously on the day of admission. The antepartum course was entirely uneventful, with an adequate pelvis as determined by pelvimetry. Past history, family history, and laboratory findings were noncontributory. Physical examination at time of admission was essentially normal, with a McDonald of 39 cm. and a vertex presentation, left occipitoposterior, floating.

During the first thirty-six hours after admission uterine contractions were irregular in occurrence and of poor quality. Following this the contractions occurred every five minutes, but were of twenty second duration. Examination revealed head dipping, and the cervix effaced was dilated 1.5 cm. Several hours later the contractions were of excellent quality every two to three minutes, lasting thirty to forty seconds, and this lasted over a period of six hours during which time she received 150 mg. of demerol, and the presenting part descended to the level of the ischial spines. It was noted, however, that no additional cervical dilatation had occurred during the latter period of active labor. Active labor continued for nine hours more without any progress of cervical dilatation or descent of the presenting part.

Because of the poor quality of contractions that ensued, and maternal fatigue, the patient was given morphia, parenteral fluids, and a rest of six hours was afforded. Active labor followed the rest interval, and examination revealed that the cervix was becoming more firm and thick. Irregularity of the fetal heartbeat prompted a vaginal examination, at which time it was noted that the cervix was about 4 cm. dilated and of the consistency mentioned previously. Upon pushing the head up a bit from its S + 1 station, the fetal heart again became regular and no further procedure was attempted. Four hours of fair labor followed, during which time the head descended below the spines, but the cervix did not dilate, and further supportive fluids were administered to the patient. The superior sagittal suture remained in the right oblique, and the position was thought to be right occipitoanterior.

Approximately forty hours after the onset of good labor the patient was delivered spontaneously of a normal living female infant weighing 3,450 Gm., who expired sixteen hours after birth. Autopsy of the infant revealed no gross cause of death. Examination of the cervix after delivery revealed that the infant had been delivered through an 8 cm. hemisecting tear of the anterior face of the cervix that ran from a superior left aspect to an inferior right lateral aspect. The os was intact and 4 cm. dilated; and the consistency was described as being "tough and undilatable." The laceration was repaired with interrupted chromic catgut sutures. The patient's postpartum course was uneventful, and the patient was discharged from the hospital on her eighth postpartum day, at which time the cervix was found to be firm, fibrous, and the laceration was healing well.

CASE 2.—M. C., Hospital No. 39233 (private patient of Dr. F. P. McNailey), was a 36-year-old white gravida ii, para 0, who was admitted to the St. Louis Maternity Hospital on April 4, 1947. From the patient's menstrual history, the estimated date of confinement was March 31, 1947. Her first pregnancy had terminated at three and one-half months by a spontaneous abortion. The patient had weighed 211½ pounds when seen during the first trimester, and at term weighed 213½ pounds. By pelvimetry the patient possessed a normal pelvis, and the routine laboratory studies were not remarkable. During the

CERVICAL DYSTOCIA, WITH SPECIAL REFERENCE TO THE FIBROUS NATURE OF THE CERVIX*

OTTO H. SCHWARZ, M.D., AND RALPH B. WOOLF, M.D., ST. LOUIS, MO.

(From the St. Louis Maternity Hospital)

NOTABLE by its absence is the well-recorded information concerning cervical dystocia in the English and American literature. The standard textbooks of obstetrics give little more than a passing mention to the condition and in the minds of many authorities little credence is given to its actual occurrence in the course of labor. When one has been confronted by the dramatic course of events such as presented in Case 1, then it is most difficult to concur with the latter group in the opinion that denies the existence of the cervical dystocia entity.

Diligent searching of the literature reveals only two outstanding reports in English on the subject during the past twenty years. Of particular significance is the fact that in considering the subject, the authors stress the importance of fibrosis of the cervix as a cause of cervical dystocia. In explaining the etiology and pathology of the condition Mathieu and Schauffler imply that the rigid and stenosed cervix is the end result of chronic irritation that causes destruction of the cervical "specialized muscle and elastic fibers" and replacement of these tissues by nonexpansile scar tissue cells. All other things being equal, the ability of the cervix to dilate is directly proportionate to the amount of muscle and elastic tissue elements as compared to the fibrous tissue content. Sackett in his report also emphasizes the rigid stenotic cervix that follows various traumas, irritations, and infections, in addition to stressing a constitutional deficiency as another general cause for cervical dystocia. He states, "Since active dilatation, retraction, and effacement of the cervix depend upon its intrinsic smooth muscle and autonomic nerves, this function may be weakened by underdevelopment, and constitutional and endocrine deficiency. It is further compromised and resisted by scar tissue replacement of the parenchyma following trauma or disease. This fibrosis also obviously hinders passive dilatation by the bag of waters and presenting part."

Such is the sentiment in the two most complete reports of the last twenty years concerning cervical dystocia. In both there is a definite implication that the origin of the condition resides in the replacement of elastic fibers and/or muscle fibers by fibrous tissue. In the recent report by Danforth, and the material to be presented below, it becomes quite obvious that the entire subject of cervical rigidity during labor must be reappraised to conform with the anatomie and histologic facts. The cervix is a priori predominantly of a fibrous nature and, therefore, it is difficult to visualize that in cervical stroma the addition of more akin fibrous tissue, from whatever cause, would lead to the occurrence of the impressive train of events recognized in some quarters as cervical dystocia.

*Presented at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

shortening of the right leg and a recently healed lower right rectus abdominal scar. The presenting part was vertex, engaged, and left occipitotransverse. Contractions were regular every eight minutes, lasting thirty seconds. Within two hours the contractions were regular and of good quality, occurring every four to five minutes, and of forty-five second duration. Vaginal examination found the membranes intact, the cervix approximately 50 per cent effaced, and 2 cm. dilated, and the head at the level of the ischial spines in a left occipitotransverse position. Amnesia and analgesia were instituted with barbiturates and hyoseine. Labor continued with contractions as previously noted, and rectal examination revealed the cervix only 1 cm. thick two hours later, while other findings were essentially as before. Because the contractions became somewhat less frequent during the sixth hour, two minims of infundin in divided doses were given, causing the resumption of vigorous labor. Vaginal examination during the seventh hour revealed the cervix completely effaced, but the other findings were as previously noted.

During the next five hours contractions were vigorous, but vaginal examination found cervical dilatation as before of approximately 2 cm., and the cervix was described as "thin and moderately soft." At this time the membranes were ruptured surgically. There followed a period of twelve hours of active labor with excellent regular contractions, during which time the cervix dilated to approximately 6 cm. and the head in left occipitotransverse position descended to a station 1 cm. below the level of the ischial spines. A note was made that the anterior lip of the cervix was becoming edematous. No progress was noted during the next two hours, and, because of signs of maternal fatigue, morphia and parenteral fluids were administered.

Irregular, infrequent, mild contractions occurred during the next eighteen hours, after which time examination revealed no change in the cervical dilatation or consistency. However, the head had rotated to a left occipitoanterior position. Fair to good frequent contractions ensued, after four hours of which the head descended to an S + 2 station with contractions and 8 cm. of cervical dilatation was present. A midforceps application was made through the incompletely dilated cervix followed by traction and Dührssen's incisions of the tough remaining rim of the cervix. A living normal female infant weighing 3,840 Gm. was then delivered by midforceps from left occipitoanterior position over a right mediolateral episiotomy that extended during the delivery through the rectal sphincter. The cervical incisions were repaired with interrupted No. 1 chromic catgut sutures. The total time elapsed since the onset of labor was approximately forty-eight hours. After an uneventful postpartum course, the patient and infant were discharged on the fourteenth postpartum day.

CASE 4.—Patient of O. S., entered St. Louis Maternity Hospital on Nov. 24, 1942. The membranes ruptured spontaneously before admission. Patient began to have contractions at 3:00 A.M. on November 24, the pains coming every three minutes, lasting sixty seconds or longer, and of strong duration. At 12:20 P.M. hyoseine was started, 2 c.c. being given over a period of three hours. In spite of thick, intense contractions, no dilatation was obtained. The cervix was effaced and there was one finger dilatation at 6:30 P.M. The lower uterine segment had apparently thinned considerably and with a rigid os present it was thought advisable to do a cesarean section. This was performed at 7:30 P.M. on Nov. 24, 1942, doing the low cervical transverse type. Results were good for both mother and infant.

Patient was readmitted on Dec. 27, 1944, in beginning labor. Examination showed the cervix long, and, in view of the fact that the cervix presented a condition similar to that presented before, an elective section was decided upon which was performed on Jan. 2, 1945, with similar good results.

antepartum period she had been given 0.060 Gm. of thyroid extract daily, and during the second and third months of the pregnancy she was given 10 mg. of pregnenolone twice a day orally because of history of previous abortion. Remainder of past history and family history were nonecontributory. Physical examination upon admission was essentially normal, with membranes intact, McDonald of 35 cm., and presenting part vertex, left occipitotransverse, floating. The patient had been having irregular uterine contractions prior to admission that continued irregular in interval and intensity for almost twenty-four hours, and she was thought to be in early labor.

During the next four days the patient had an occasional mild contraction, and the membranes ruptured spontaneously on the fifth day following admission. Three days after the membranes had ruptured vigorous labor began. Vaginal examination at this time revealed that the presenting part was floating and the cervix was 2 cm. long and admitted a fingertip. The labor continued unabated for seventeen hours, and a vaginal examination was done. The head was engaged to 1 cm. above the ischial spines, left occipitoposterior, and the cervix was effaced except for a thick margin, and there was 4 to 5 cm. dilatation present. Analgesia and amnesia was commenced at this time and maintained for the duration of labor using demerol and hyoseine. Labor continued vigorously with excellent regular contractions every three minutes lasting fifty to sixty seconds for three and one-half hours longer, at which time findings by vaginal examination were as before. Kielland forceps were applied through the partially dilated cervix, and the head was rotated to a left occipitoanterior position and held in that position without traction for the next one and one-half hours while labor progressed. The forceps were removed, and excellent contractions continued for another one and one-half hours, when vaginal examination showed the head to have reverted to the left occipitoposterior position with the most dependent portion just below the level of the ischial spines. The cervix was approximately 6 cm. dilated, and a gentle attempt was made to increase the dilatation normally. Two hours later vaginal examination was again done. The cervix possessed a "good" rim, and the left occipitoposterior head had made no further descent. Kielland forceps were again applied through the incompletely dilated cervix, and the head was rotated to an anterior position and held while the anterior lip of the cervix was gradually pushed over the occiput manually. The Kielland forceps were removed and Schwarz forceps were applied. Delivery was effected by low forceps from left occipitoanterior position over a right mediolateral episiotomy twenty-eight hours after the onset of active labor. The infant was a normal male weighing 3,740 Gm. who required no resuscitation. Examination of the lower genital tract after delivery revealed no evidence of injury. The postpartum course was uneventful, and the patient and infant were discharged from the hospital on the tenth postpartum day.

CASE 3.—G. H., Hospital No. 50583 (private patient of Dr. W. D. Hawker), was a 33-year-old primigravida who was admitted to the St. Louis Maternity Hospital on April 20, 1946. From the patient's menstrual history the estimated confinement date was April 23, 1946. When first seen by her obstetrician in February, 1946, physical examination revealed a tender 3 inch myoma in the region of the right cornua of the uterus. Also, the patient had a 2 inch shortening of the right leg as a sequela to anterior poliomyelitis. In November, 1945, a myomectomy had been performed at a Naval Hospital in California. Pelvic measurements were essentially normal. The remainder of the antepartum course, past history, and family history were nonecontributory. Routine laboratory procedures were not remarkable.

Upon admission to the hospital, the patient had had uterine contractions for two hours. Physical examination was normal except for the presence of

more satisfactorily. A very small incision was made (not more than 12 to 13 cm.), and on closing, the uterus fell easily into the abdominal cavity, indicating that it was not a normal-sized uterus. It was suspected at that time that the patient had an infantile uterus and, hence, a primary inertia. This contention was proved without a doubt eight weeks post partum, when examination of the uterus showed it to be definitely smaller in size than a normal nulliparous uterus.

Comment

From the above-mentioned statements it is obvious that in the discussions of the subject it revolves itself entirely on the fibrous nature of the cervix, as put so well by Danforth. Irrespective of what clinical ideas we wish to present on the functional rigidity of the cervix, it would have no place or weight unless Danforth's recent findings were thoroughly discussed. So, therefore, this presentation in short is concerned chiefly with the confirmation of Danforth's findings, to which we can say we perfectly agree.

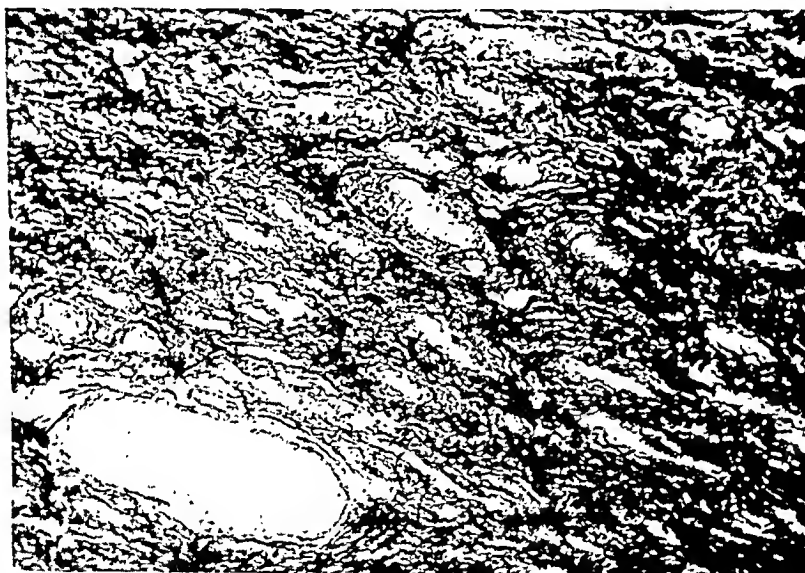


Fig. 3.—Multiparous uterus, aged 50 years. Section near external os. Cervical glands showing black fibular structure entirely connective tissue.

We were a little doubtful of whether the use of old material would suffice for an exact study, but with previous experiences with old fixed material for the body of the uterus, we thought we might try. Amazingly, the material stained perfectly, and as a result we were able to confirm Danforth's work entirely. Of course, our work, as a result of time, was limited to a study of 19 cases. However, we were able to perfectly reproduce our findings with colored photomicrographs. To make a confirmation of Danforth's findings we can do no better than to quote him verbatim.

"The Nonpregnant Uterus.—

"A. Intrinsic structure of cervix and isthmic segment: The appearance of the cervical wall in routine hematoxylin and eosin stains is familiar. It is composed of interlacing strands of fibrillar tissue which take a light pink stain, show

CASE 5.—Patient of O. S., entered St. Louis Maternity Hospital on March 24, 1947, with a breech presentation confirmed by x-ray. Her estimated date of confinement was March 17, 1947. Patient had constant Braxton Hicks contractions for two weeks prior to operation. The cervix was long, pelvic floor very resistant. Both the puborectal portion and the iliac portion of the levator ani muscles were very prominent. The patient was seen on July 27, 1946, for



Fig. 1.—The entire section of uterus of a 2-year-old child. Fig. 2 shows the contents of the cervical structure.



Fig. 2.—Van Gieson stain—showing cervical canal, fine black fibular structure, entirely connective tissue.

the first time, having missed her period just two weeks previously. The uterus was soft, but not appreciably enlarged. Pregnancy was suspected which proved correct, so that the onset of the pregnancy was assured.

On March 30, 1947, a low transverse incision was made for section. During the operation it was noted that exposure of the lower transverse incision was not as good as under ordinary circumstances, and after the delivery of the infant the uterus was brought through the abdominal incision to render suturing

cervix. Rarely, they appear in small bundles near the central portion of the tissue, being either isolated or continuous with the muscular tissue superior to the cervix. The inconstancy of such central bundles and their attenuated appearance when they are present make it unlikely that sphincteric possibilities could be attributed to them.

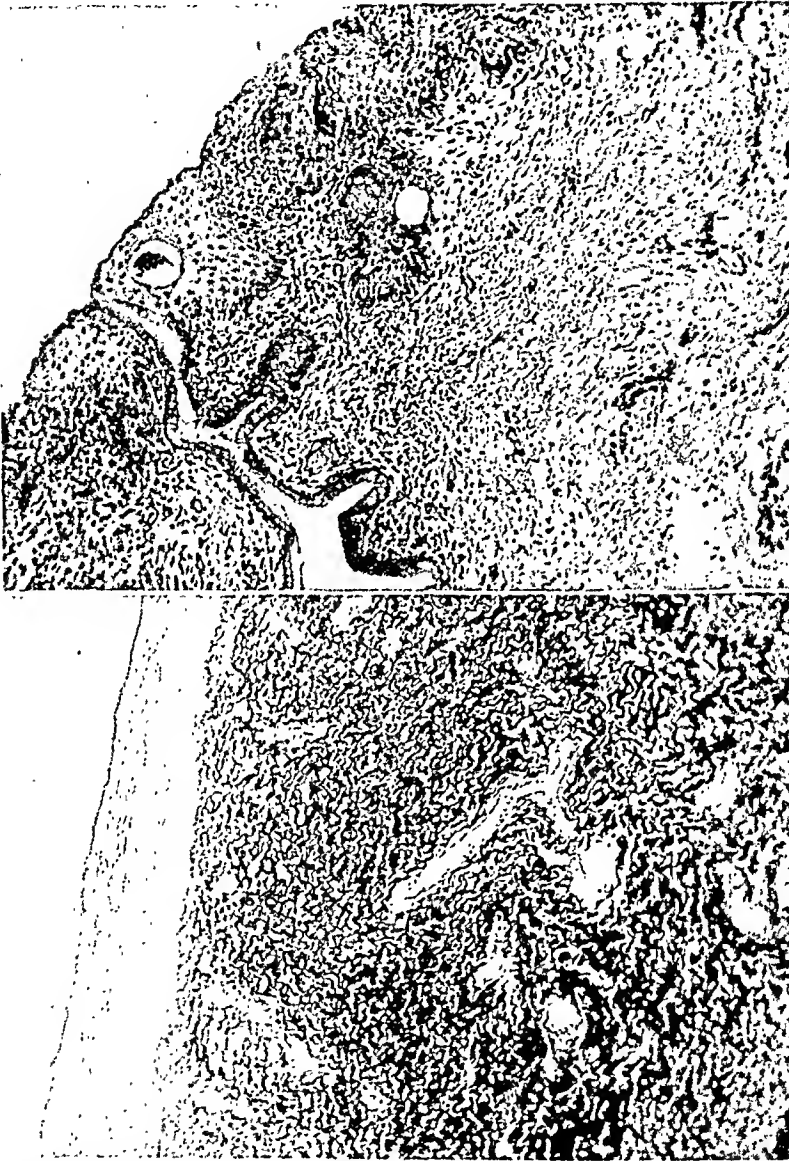


Fig. 6.—Hematoxylin-eosin stain near external os.

Fig. 7.—Practically same field showing practically entire connective tissue with ligamentous squamous epithelium to the left.

**Stains for elastic tissue showed the presence of minute and, to the author's opinion, insignificant amounts of these fibers. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. As one might expect, they were most abundant in and around the walls of the larger blood vessels. Elsewhere they constitute but a fraction of 1 per cent of the total fibrous tissue of the cervix. Superior to the cervix they were also sparse, being for the most part limited to the outer third of the uterine wall and located in the fibrous tissue separating the muscle bundles.

no tendency to strata formation, and, except for the edema which accompanies many cervical lesions, show no significant differences from the uterine wall above the cervix. In some areas the tissue resembles fibrous tissue, in others, smooth muscle. When employing this stain alone, absolute differentiation throughout the entire cervix is considered as impossible.



Fig. 4.—Same section taken well up in the cervix showing muscular structure beginning to appear, perhaps 30 per cent.

Fig. 5.—Same cervix outer third higher up, showing beginning predominance of muscular structure.

“A very striking picture is obtained by use of differential stains for fibrous tissue and smooth muscle. The basic structure of the cervix is found to be fibrous connective tissue. In many specimens virtually no smooth muscle can be found. From this extreme, one passes to other specimens in which moderate amounts of muscle are present; occasionally this may reach as much as 40 or 45 per cent though ordinarily it does not exceed 10 or 15 per cent. When muscle does appear in cervical sections, its distribution shows great variability. Ordinarily the muscle fibers are scattered at random throughout the substance of the

bearing age. The cervixes were quite normal, the fundamental tissue was fibrous, the smooth muscle was sparse and widely scattered, and the fibromuscular junction abrupt.

“II. *The Pregnant Uterus.*—

“A. *Intrinsic structure of cervix and isthmus during early pregnancy:* Specific estimates of hypertrophy and hyperplasia of the muscle and fibrous tissue elements are not possible with the techniques which have been employed here.

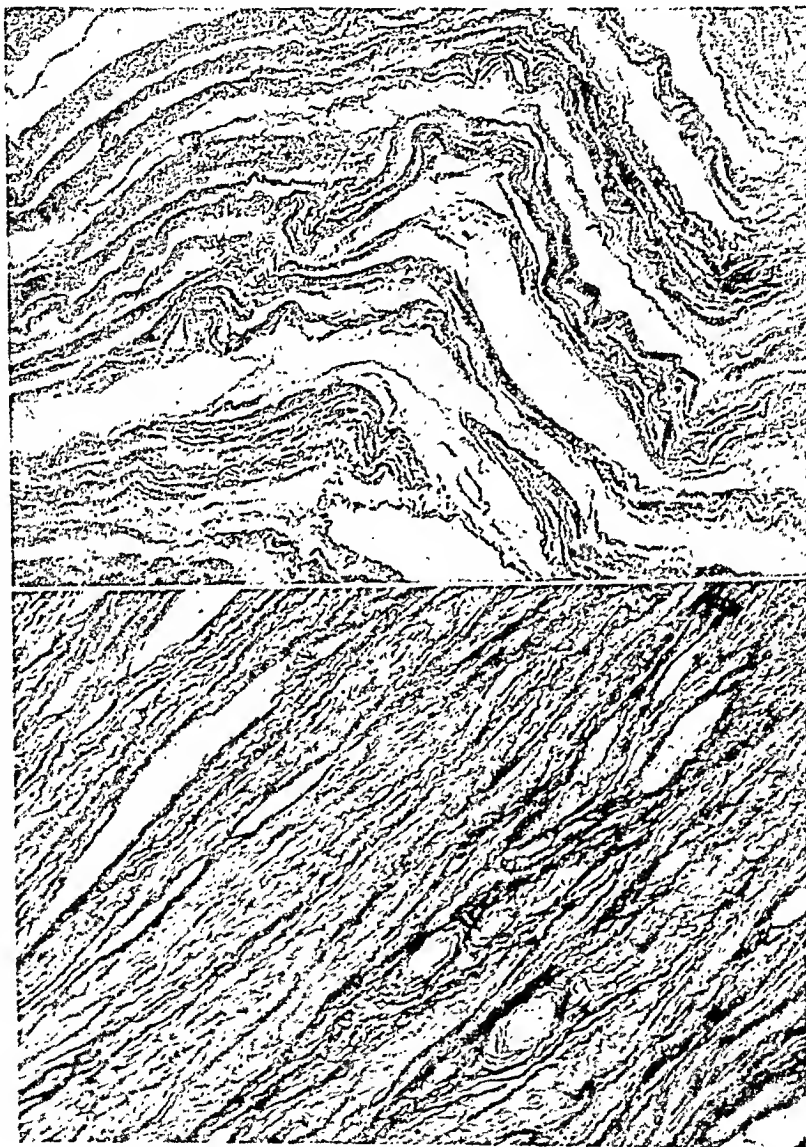


Fig. 10.—Lower uterine segment of same specimen showing slight transition to muscular structure.

Fig. 11.—Higher up showing transition through predominance in muscular structure.

There is the distinct impression of the enlargement of both of these elements and of an increase in their number. Also, the presence of edema in the pregnant specimens is quite definite.

“By the means which have been used, it is not possible to confirm the reported changes in elastic tissue during pregnancy. Elastic fibers are present in the same (negligible) quantity as in the nonpregnant specimens, and with the

"The fibromuscular junction: As one ascends the cervix to the region of the histologic internal os, a level is reached where the predominance of fibrous tissue ceases, giving way to smooth muscle. The nature of the transition zone is variable. Sometimes it is abrupt and immediately complete, while in others it may be extremely gradual, occurring almost imperceptibly over the course of 5 or (at most) 10 mm. In some instances the plane of the transition is straight across the uterine wall; but more often the line is a wavy one. It is of interest that not only may the nature of the transition line vary in different portions of



Fig. 8.—Gross specimen cervix of about twenty weeks pregnancy.

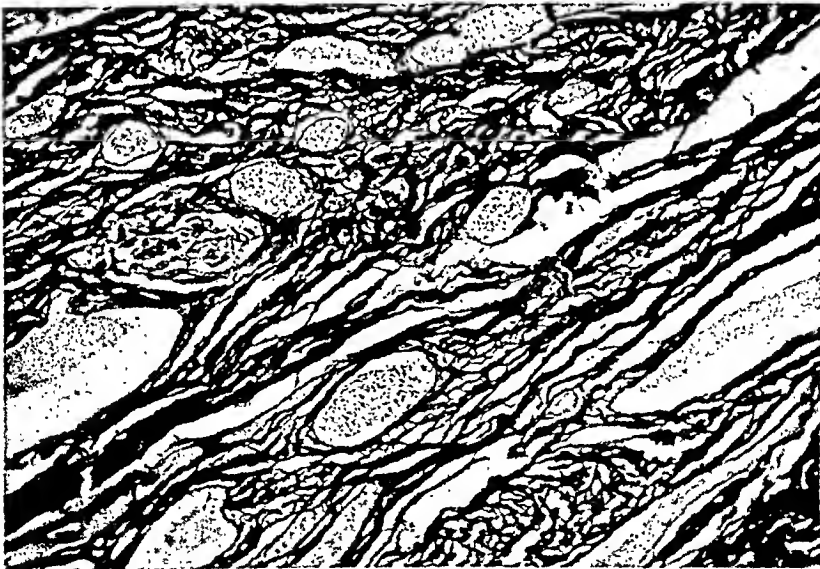


Fig. 9.—Cervix from Fig. 8 showing increased vascularity and connective tissue entirely prominent.

the same cervix, but also its level with respect to the external os may vary as much as 6 or 8 mm. In these specimens there was no definite correlation of the patient's age, parity, and the local cervical lesion with the nature of the fibromuscular junction. In general, the transition was less gradual in the more normal specimens. Five uteri were obtained from nulliparous women of child-

We have included only a few case histories of outstanding cases of functional rigidity as the whole subject revolves on Danforth's new findings. We had planned originally to go into detail concerning uterine innervation and the effects of endocrine reaction as regards the softening of the lower uterine segment and cervix. There is no doubt that there may be several contributed factors, but essentially it must now be considered that the fundamental fibrous nature of the cervix plays the most important part.



Fig. 12.—Gross specimen twenty-eight weeks pregnant showing complete cervical canal and development of lower uterine segment.

For the following we are indebted to Dr. M. A. Roblee of St. Louis, who has a wide experience in this field.

“Conization of the Cervix.—

“It is difficult to evaluate cervical dystocia and trauma to the cervix at childbirth in the previously coned cervix. Most patients that have had conizations are multiparous and are not desirous of more children as a rule. Their average age would be past the mid thirties. We have averaged approximately 100 conizations a year, and out of this number in the past sixteen years we had approximately 150 observed pregnancies in women who had had conization of the cervix. Surprisingly little trouble has developed. In a study of cervical dystocia and Dührssen incisions of the cervix, no references were made to previously coned cervixes as being a possible factor.

“Although we practice and teach that conization should not be performed during the active childbearing age, there is little clinical evidence in our hands to support this conclusion. One reason for this is undoubtedly the technique of not re-entering the cervical canal after the original cone has been removed. A different electrode designed solely to undercut the hypertrophied cervical lips without burning again the endocervical portion of the cervix reduces the glandbearing area of the cervix without damaging the fibrous muscular junction of the cervix as described by Danforth in a recent article. Danforth points out that as pregnancy develops, the cervix becomes the lower portion

same haphazard arrangement except with reference to the blood vessels. Elastic stains were available in the corpus in only two of the pregnant specimens. In these the fibers were limited to the outer third of the uterine wall, being interspersed among the fibrous connective tissue which separates the muscle bundles. They were considerably more numerous in the tissue immediately above the cervix.

"With the exceptions of greatly increased vascularity and edema, the fundamental structure of the cervix was found to be similar to that of the nonpregnant specimens. The basic tissue is fibrous. Varying quantities of smooth muscle are present, amounting to from 2 to 40 per cent, with an average of about 10 per cent. The distribution of muscle is likewise variable, though the presence of small bundles in the central portions of the tissue is somewhat more common. When they do appear, the bundles are heavily interspersed with fibrous tissue, and appear to have insignificant splineteric possibilities."

Our study consisting of nineteen uteri; two infantile uteri (one at 14 years of age), three pregnant uteri (one at 12 weeks, one at 20 weeks, one at 26 to 28 weeks), the remaining material was selected at random. The results from this study coincide entirely with the more extensive work of Danforth in practically every detail, as our illustrations will clearly bring out. In our presentation, we use colored slides, but in publication we shall use black and white illustrations with proper explanation.

In studying this material we used hematoxylin-eosin, Van Gieson's stain, Masson's stain, and orcein. Stains as follows:

Masson Stain

Solution A	
Acid fuchsin	0.6 Gm.
Poncern De Xylidine	1.4 Gm.
Distilled H ₂ O	205 c.c.
Acetic acid (glacial)	2 c.c.

Solution B	
Phosphatungstic acid	2 Gm.
Distilled H ₂ O	200 c.c.

Solution C	
Acetic acid (glacial)	4 c.c.
Distilled H ₂ O	200 c.c.
Light green 1 per cent	1 Gm.

Orcein Stain

Orcein	1 Gm.
Absolute alcohol	100 c.c.
Hydrochloric	1 c.c.

Van Gieson Stain

1 per cent stock solution picro fuchsin	1 Gm.
Acid fuchsin	5 c.c.
Saturated solution picric acid	100 c.c.

We used these stains separately, and particularly Orcein for elastic tissue, knowing well from previous experience that elastic tissue played a most minor part in the bulk of uterine structure.

We also realized fully that the innervation of the uterus may play a part in action concerning the dilatation of the cervix, but as knowledge of uterine innervation has not as yet been cleared, especially as it concerns the motor nerves very little can be said emphatically. However, Masters of our service has given this subject much study in connection with work on caudal anesthesia, and we are indebted to him for the following:

“The question of uterine nerve supply is one of the major unsolved problems in the field of gynecological anatomy. The entire subject is surrounded by conjecture based on a minimal amount of factual information.



Fig. 15.—The uterus of a 14-year-old girl showing vagina, cervix, isthmus, and body.



Fig. 16.—From cervix showing pregnancy, entirely connective tissue.

“As the result of the pioneer work of Cleland, we know something of the sensory component of the uterine nerve supply, but the motor innervation of the uterus is, as yet, unresolved.

“The basic nerve supply to the uterus is through the autonomic system as perhaps best demonstrated by the opposing Kuffer forces of the sympathetic and parasympathetic systems supply the uterus with both afferent and efferent nerve fibers. The sensory fibers run through the ganglions of the eleventh and twelfth thoracic segments to synapse through the dorsal root ganglions of those levels. The motor inertia is as previously stated, unsolved. A theory

of the uterus and the muscular fibrinous elements contribute to effacement and dilation of the cervix.

"Of the approximately 150 cases of observed pregnancy following conization, ten might be classified as having varying degrees of cervical dystocia, however, none required incisions. Dilation progressed surprisingly rapidly although from four to six hours of labor were required to thin out and obliterate the cervical canal before dilation occurred. Eight cases received manual dilatation of the cervix after effacement.



Fig. 13.—Cervix low down from Fig. 12 showing pregnancy entirely connective tissue.

Fig. 14.—Taken high up from Fig. 12 showing a mixture of muscle tissue to fibrous tissue—about 50-50.

"In regard to fertility after conization, it has been observed that when the chronic endocervicitis is cleared up by a subtotal removal of the gland-bearing area which permits a normal cervical secretion to follow conization, conception readily occurs (in the absence of other lesions) and none of these cases acquired cervical dystocia."

motor innervation and, of course, have widely substantiated the source of the sensory component of the uterine nerve supply.

"Experience in St. Louis Maternity Hospital based on better than fifteen hundred caudal analgesia attempts have certainly overwhelmingly verified the source of sensory innervation of the uterus to include the eleventh thoracic nerve root as its highest component."

Caudal analgesia levels taken as high as the fourth or sixth thoracic nerve roots have frequently slowed or even stopped labors, particularly when initiated early in the first stage of labor. This clinical observation would tend to lend credence to the assumption that the motor innervation to the fundus takes its origin (in part) from sources higher than the tenth thoracic nerve root. However, while the clinical observation of slowing first stage 1 of labor with high caudal analgesia levels is undoubtedly well founded, the same type slowing or stoppage of labor with a heavy twilight early in the first stage 1 has also been frequently noted, though to a lesser degree.

We do not agree with Ilingran and his co-workers in the belief that controlled caudal analgesia levels shortens stage 1 labors. In theory this reduction in the length of time necessitated by stage 1 labors should occur, because a level sufficient to control the distress of contractions (T-11) would of necessity have inactivated the theoretical parasympathetic motor component to the lower uterine segment and cervix (S2-S4). We have seen no real over-all induction in stage 1 labors. As a matter of fact, it is our opinion that stage 1 labors are moderately prolonged under caudal analgesia.

Also the question of what part the ovarian hormones play in the softening of the cervix is not fully understood but there can be no question that they must play a part, especially progesterone. In face of functional rigidity in the cervix, it is quite possible that their unbalance, or the deficiency of one or the other or possibly both may play a part, especially in cases of rigidity in the elderly primipara due to the much later date that these cases first receive this softening.

Conclusions

1. Functional rigidity of cervix in the elderly primipara is due to its fibrous nature, having not been previously stimulated by the effects of previous hormone physiology.

2. Annular cervical detachment takes place at the fibromuscular junction, as determined by the study of tissue from two such cases.

3. Amputation of the cervix leads to premature labor. Andebert and Pinard quote twenty-four cases of pregnancy in cases of this type in sixteen women, only five going to term. Obviously with the fibrous cervix removed, there was no structure to keep the uterus from dilating.

4. The cervix after conization, as quoted from Dr. Roblee in over 1,500 conization cases, who states that pregnancy occurred in 10 per cent, only eight cases in 150 gave any cervical difficulty, only a little manipulation, no incisions or sections.

based on clinical observations of DeLee places the origin of the motor supply to the fundus above the level of the tenth thoracic vertebra and presumes a downward pathway for motor fibers through the aortic plexus to the ganglion of Frankenhauser. Further nerve supply of questionable motor component is believed to arise from a combined sympathetic and parasympathetic source.

Fig. 17.

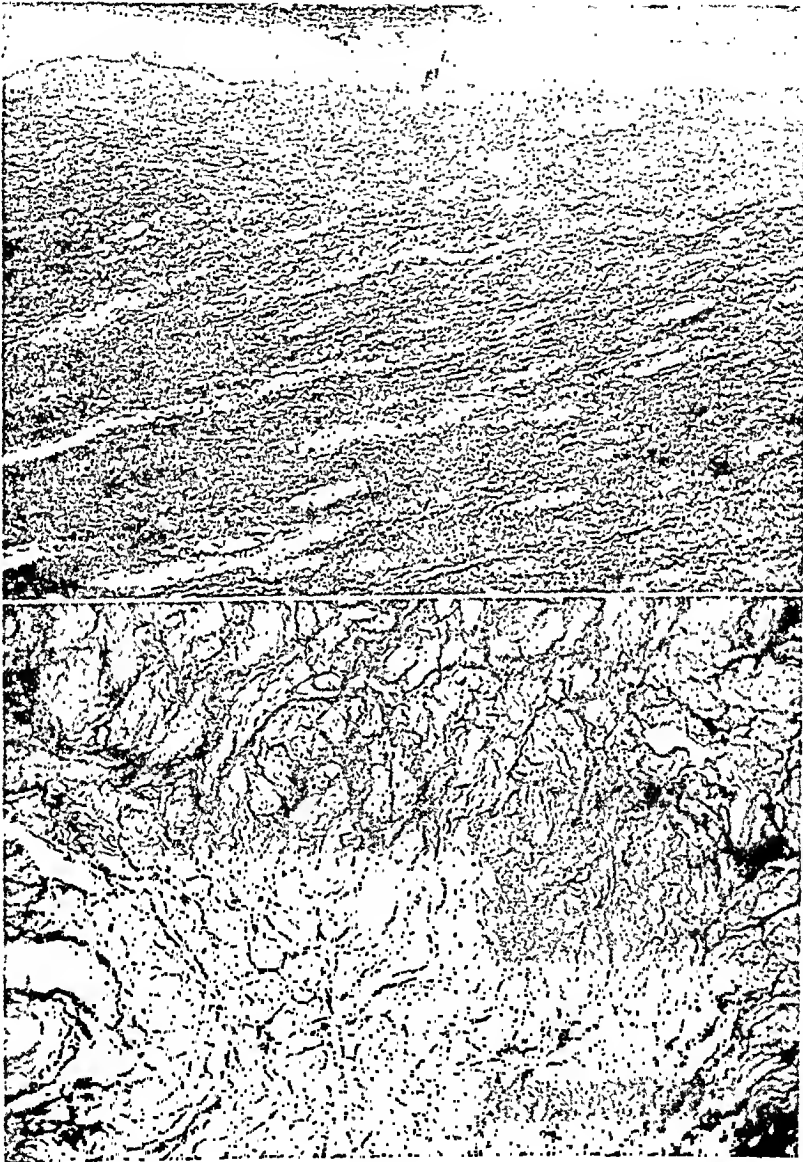


Fig. 18.

Fig. 17.—From isthmus showing a mixture, but connective tissue is still most prominent.

Fig. 18.—From Fig. 15 from body of uterus showing prominence of muscle structure in that region.

As stated above the sympathetic component is of unknown origin and the parasympathetic plexus arises from the second, third, and fourth sacral nerves. This innervation is believed to control the lower uterine segment and cervix. Visceral efferent fibers believed to be motor to the longitudinal muscle fibers of the lower uterine segment and to the circular muscle fibers of the cervix have origin in the sacral parasympathetic plexus.

“Actual clinical experience both in following closely the progress of labor, and the definitive use of caudal analgesia have failed to answer the question of

vaginal vault. There one can, in not too abnormal uteri, hit a fairly good superficial cleavage plane which can be followed for about one centimeter.

DR. SCHWARZ (Closing).—In answer to Dr. Rueker's question about the constriction ring and why one cervix will dilate and another will not, I think the knowledge on that point is rather vague, but there can be little doubt that it must be due to estrogenic stimulation plus progesterone. Now whether this stimulation is adequate or due to the normal stimulation of a rather toughened cervix, of course no one can say.

So far as rings of musculature in the cervix are concerned, Dr. Danforth has proved them nonexistent. I could not find any signs of encircling musculature. The cervical muscle is of an infiltrating type. It comes on the outer third of the uterus a little earlier but for no appreciable depth. On the other hand, there is an admixture of the substances and there can be no question about the softening of the isthmus during pregnancy which produces a Hegar's sign. The very fact that this occurs would indicate to me that the reason the cervix does not soften along with the isthmus is because of this fact.

Another point I wanted to make is the fact that formerly the so-called amputation of the cervix was done very frequently. I have seen two cases where the patient carried the pregnancy to the fourth, fifth, or sixth month, and then went into labor. Twenty-four cases have been reported by others and in only five instances did the patient go to term. The explanation of that is now simple to me, for they merely cut away the fibrous tissue and there was nothing to hold the pregnancy in.

We wish to express our thanks and deep appreciation to Miss Geraldine Brennan for her staining of the specimens, and to Mr. K. Cramer Lewis for his development of the colored photomicrographs which entirely helped to make this contribution.

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2. Mathiew, A., and Schauffler, G. C.: *AM. J. OBST. & GYNEC.* 16: 390, 1928.
3. Sackett, N. B.: *AM. J. OBST. & GYNEC.* 42: 248, 1941.

Discussion

DR. M. PIERCE RUCKER, Richmond, Va.—Dr. Danforth, by his study of frozen sections of the monkey's uterus in various stages of labor, has already caused me to change my ways in the management of the third stage of labor. I was in hope that he and Dr. Schwarz would explain to me in words of one syllable why some cervixes, with presumably the same structure, dilate and some do not.

Sackett, in a paper that he read before the Richmond Academy of Medicine several years ago, defined cervical dystocia as the failure of the cervix to dilate or to be effaced, (when there is no obvious mechanical reason therefor), within a reasonable time despite frequent and forceful contractions of the uterus. He reported 86 cases, a frequency of 1.05 per cent. Under etiology he says that those who admit the existence of cervical dystocia offer two general explanations of its origin. The first points to a constitutional deficiency, manifested by obesity, lack of feminine habitus, endocrine dyscrasia, disturbance of menstruation and fertility, and maldevelopment of the genital tract.

The second theory stresses rigidity and stenosis of the cervix as a result of fibrosis following operative or obstetric trauma, abortions and infections.

From the work presented today it would seem that the cervix has normally enough fibrous tissue to prevent its dilatation, if fibrous tissue were the answer. Why any cervix dilates is the important question. All of us have seen, I am sure, cervixes destroyed by radium and the normal structures replaced by dense fibrous tissue. I recall one such case in which the entire vaginal vault was a mass of scar tissue with merely a little depression to represent the cervix. This patient had a precipitous labor a week before the time set for her cesarean section.

I am convinced that a great number of cervixes do not dilate because of a constriction ring which firmly fixes the baby to the body of the uterus. In my experience, this occurs in about once in 90 cases. I have not been impressed that a rigid cervix has been a factor except in the very exceptional case. I have resorted to Dührssen's incision once in the past twenty years.

The work of Drs. Schwarz and Woolf explain why, immediately after delivery, the cervix hangs like a loose crinkled cuff with no evidence of contractility. It does not show why it dilates during normal delivery and fails to dilate in cervical dystocia.

DR. KARL MARTZLOFF, Portland, Oregon.—Dr. Schwarz' slides are beautiful and disturbing, because they upset one's previous ideas concerning the mesodermal structure of the cervix. Tonight Dr. Schwarz confirms Dr. Danforth's recently published observations.

I would like to ask whether Dr. Schwarz has been able to prove that the cervix possesses an external longitudinal layer of musculature as described by Stieve; also whether his observations confirm those of Dührssen, who I believe described an outer layer of connective tissue? I would also like to ask what method of fixation was used on his material; if his material is old; whether the age of the material and the fixation fluid would have any effect on the differential staining? These questions arise, because in otherwise fibrous areas, Dr. Schwarz' slides show clearly the musculature of the blood vessels. It occurred to me that the vascular musculature might possibly retain this differential staining property while musculature otherwise situated might not. Using maceration methods, I have never been able to dissect out any tissue layers in the cervix except right at the place where the portio attaches to the

by cesarean section. Simple rupture of the membranes was the common alternative method of treatment to cesarean section, and was done in thirty-two cases (30 per cent). In two instances scalp traction was applied after rupturing the membranes. In twenty patients the onset of labor was spontaneous with spontaneous vaginal delivery. All of these were of the marginal variety except one which was classified as partial. Those treated by version were admitted in labor with dead or nonviable infants, in two of whom the children were presenting transversely. In these cases a foot was brought down into the vagina, and full cervical dilatation awaited before completing the delivery. This was a method employed to empty the uterus of patients in labor with dead or non-viable children, and was not a procedure of choice in the selective management of placenta previa.

Diagnosis

The diagnosis was established by determining the location of the placenta either at the time of cesarean section or on vaginal examination. An attempt at diagnosis by various methods of x-ray examination was made in sixty-four of these patients. In fifty-one the x-ray diagnosis was positive for placenta previa, while in thirteen the x-ray findings were inconclusive.

Maternal Mortality

There was one maternal death in the one hundred and five cases (0.95 per cent). This was a multipara admitted to the hospital in her eighth month of pregnancy with a dead fetus. There had been persistent bleeding at home for three weeks, during which time her local physician had made numerous vaginal examinations, following one of which an alarming hemorrhage occurred. The patient was then sent to the hospital. At the time of admission she was almost exsanguinated and had a temperature of 101° F. After reacting following transfusions, a vaginal examination was done and revealed a partial previa. The membranes were ruptured artificially and an easy vaginal delivery followed. The patient died on the fifth postpartum day of a generalized infection, which was confirmed by postmortem examination. This death occurred before the era of chemotherapy or antibiotics. This is obviously a preventable death, due to the error of performing repeated vaginal examinations in the home in a case of antepartum bleeding, and for failure to replace blood loss or to send the patient to a hospital promptly, where appropriate management could have been instituted.

Fetal Mortality

Twenty-nine children of these one hundred five patients did not survive. Fourteen were stillborn and fifteen died neonatally, a fetal mortality of 28 per cent. Of the seventy-four patients who were either successfully carried to term or who did not have their initial bleeding until the child was of term size, eight babies (10 per cent) were lost. On the other hand, of the thirty-one patients who either went into labor spontaneously or in whom the pregnancy was terminated before the child attained a size of 2,500 Gm., twenty-one babies (68 per cent) were lost.

THE EXPECTANT MANAGEMENT OF PLACENTA PREVIA*

TIFFANY J. WILLIAMS, M.D., CHARLOTTESVILLE, VA.

(From the Department of Obstetrics and Gynecology, University of Virginia)

THE maternal mortality in placenta previa has been appreciably reduced in the past decade mainly by the replacement of blood loss by adequate transfusions of whole blood. On the other hand, fetal mortality remains high, due in great measure to prematurity. In order to improve the fetal results, it is necessary to carry these patients closer to term. Ample, properly matched blood, and caution in the use of vaginal manipulations may make it possible to continue the pregnancy until the child is larger, and so increase the fetal salvage. Recent reports by Macafee¹ and Johnson² have suggested this possibility and have cast doubt upon the correctness of the dictum that there is no expectant treatment of placenta previa.

In the present report we wish to present the results in 105 cases of placenta previa seen at the University of Virginia Hospital during the past eleven years. Forty-one of these patients were treated in an expectant manner. Obviously, there can be no expectant treatment once labor has begun. Likewise, if the patient is at or near term, there is no advantage in attempting to prolong the pregnancy.

Of the 105 cases of placenta previa twenty-one were classified as central, twenty-three as partial, and sixty-one as marginal.

TABLE I. TYPE OF PREVIA

Central	21
Partial	23
Marginal	61
Total	105

TABLE II. METHOD OF TREATMENT AND DELIVERY

METHOD	NO.	PER CENT
Cesarean section	44	42
Rupture of membranes	32	30
Scalp traction after rupture of membranes	2	2
Spontaneous onset of labor and vaginal delivery	20	19
Version	7	7
Total	105	100

The most common method of treatment for delivery was cesarean section (42 per cent), with the operations divided equally between the classical and low cervical types, twenty-two of each. All cases of central previa were delivered

*Read (by invitation) at the Seventieth Annual Meeting of the American Gynecological Society, at the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

†Dr. Williams died August 19, 1947. Proof corrected by Dr. W. N. Thornton, Jr.

poor and the child too small to survive. In addition, vaginal examinations, particularly if packing is placed in the vagina and around the cervix, carry the added risk of infection, as is evidenced by our one fatality.

Helpful information in diagnosis may be obtained by abdominal examination. Usually the presenting part does not engage satisfactorily in the superior strait of the pelvis, if any appreciable degree of placenta previa is present. The high unengaged presenting part or an abnormal presentation, such as transverse or oblique, in the presence of antepartum bleeding, is strongly suggestive of placenta previa. An attempt at diagnosis by some method of x-ray examination may be undertaken if the condition of the patient permits.

If the patient is at term or has an apparently viable baby, a method of delivery may be selected as soon as the general condition of the patient permits. If the presenting part is not engaging in the pelvis, vaginal examination is apt to be particularly hazardous. In such instances we often omit vaginal examinations, and when delivery is decided upon, if the presenting part is still floating above the pelvic inlet or presenting abnormally, we deliver the patient by cesarean section. It is possible that the occasional patient treated in this manner may have a premature separation of a normally situated placenta, or some uncommon condition, which may have caused the bleeding. We believe, however, that an abnormal presentation with a viable baby is more safely delivered by cesarean section, so, while the preoperative diagnosis may at times be incorrect, it is felt that the patient received the wisest treatment.

If the presenting part is dipping into the pelvis and delivery has been decided upon, a vaginal examination is done. The condition of the cervix is gently determined, and the lower segment lateral to the cervix is palpated. When the presenting part cannot be readily felt through the tissues lateral to the cervix, it suggests the presence of placental tissue in the lower segment. If the cervical canal is short and admits the finger, the region around the internal os is cautiously felt. In the event placental tissue is palpated, every effort is made to avoid disturbing its attachments. If the cervix is short, soft, and patulous, and a portion of the internal os is not covered by the placenta, the membranes are ruptured. When the cervix is not favorable for vaginal delivery, or if the internal os is completely covered by placental tissue, delivery is then accomplished through the abdomen.

In the event that the child seems too small to survive, and if labor has not begun, an expectant attitude may be adopted. A gentle examination and inspection of the vagina and cervix may be done to eliminate the possibility of some infrequent cause of bleeding such as ruptured varices, or cervical tumors, but the cervical canal should not be explored. These patients should be kept under observation, preferably in the hospital, although we have permitted some of them to return home, with instructions to abstain from sexual intercourse, to permit no vaginal examinations, and to return to the hospital with the first recurrence of bleeding. Forty-one of our patients were kept under observation for periods of time varying from two days to three months in an effort to obtain a child which would survive. Fourteen of these patients had two or more periods of hospitalization for recurrent episodes of bleeding. Of these forty-one patients,

Seven patients went into spontaneous labor prematurely, and of these seven premature babies, five died neonatally. Thus, even though an expectant attitude may be adopted, some of these patients will go into spontaneous premature labor with its adverse effects on the fetal results.

TABLE III. FETAL RESULTS

METHOD	NO.	TERM 74			PREMATURE 31		
		LIVED	DIED		LIVED	DIED	
			STILL- BORN	NEONA- TALLY		STILL- BORN	NEONA- TALLY
Spontaneous	20	12	1	0	2	0	5
R. of M.*	34	22	4	1	4	2	1
Cesarean	44	32	0	1	4	0	7
Version	7	0	1	0	0	6	0
Total	105	66	6	2	10	8	13
			8 or 10%		21 or 68%		
Total Fetal Deaths 29 or 28%							

*Rupture of membranes with two cases with scalp traction.

The recent reports in the literature show similarity of results in placenta previa. Some of these are shown in Table IV. The maternal mortality averages

TABLE IV. RECENTLY REPORTED RESULTS IN PLACENTA PREVIA

AUTHOR	NO. OF CASES	MATERNAL DEATHS		FETAL DEATHS*	
		NUMBER	PER CENT	NUMBER	PER CENT
Macafee ¹	174	1	0.57	41	23.0
Davis & Campbell ³	325	2	0.6	104	31.6
Yepes & Eastman ⁴	111	1	0.9	52	46.8
Williamson & Greeley ⁵	162	5	3.1	50	31.1
Seeley ⁶	250	7	2.8	91	34.6
Johnson ²	79		0.0	26	31.0
Scott ⁷	191	5	2.6	56	29.6
Totals	1,292	21	(1.6)	420	(32.5)

*No correction.

1.6 per cent, whereas the fetal loss is 32.5 per cent, or approximately one out of three babies is lost. The earlier methods of treatment resulted in 5 to 10 per cent maternal deaths and about 40 to 60 per cent fetal deaths.

Treatment

The first essential in the treatment of antepartum bleeding is the determination of the blood type and Rh factor. Ample properly matched blood should be available and should be given in adequate quantities, dependent on the amount of blood loss and the condition of the patient.

Placenta previa requires hospitalization for diagnosis and treatment. Attempts to determine the cause of antepartum bleeding by performing vaginal examinations in the home do not improve the outlook for the mother or her baby. Pelvic examinations may cause more hemorrhage by separating additional areas of the placenta. Occasionally, these examinations seem to start uterine contractions, so that some definitive type of treatment must be employed because of the presence of labor, even though the condition of the patient may still be

from England and this country. These studies show that the maternal death rate by the use of copious transfusions, and antibiotics and sulfonamides has been reduced to approximately 2 per cent. The major problem is that of a high fetal mortality which in his collected series is somewhat over 30 per cent. In the forty cases in which Dr. Williams was able to use the expectant treatment and thereby bring these babies closer to full term, his mortality rate was under 12 per cent, and in this group not one mother was lost. These amazingly good results attest the soundness of his procedure. Too often the obstetrician in his anxiety for the welfare of the mother is prone to disregard the rights of the child to a better chance of survival. I must confess, however, that I am in diametric disagreement with Dr. Williams in allowing patients who have had one or more hemorrhages from placenta previa to leave the hospital before delivery. Even though the patient is in the hospital, an alarming amount of blood can be lost before adequate measures can be taken for transfusion and for control of hemorrhage.

DR. WILLIAM C. DANFORTH, Evanston, Ill.—Some fifty years ago Jaggard, the predecessor of DeLee at Northwestern, enunciated the doctrine that "there is no expectant treatment for placenta previa." The increase in hospitals for the care of parturient women and the experience of obstetricians has modified this dictum to some extent, although still, in most cases, immediate and decisive therapy is called for.

As to the active treatment of placenta previa, I agree with the essayist almost completely. His recommendation that all preparation for restoration of blood loss be made in advance is sound doctrine. A Wassermann or Kahn, the determination of the Rh factor, cell volume, blood typing, and crossmatching should all be done at once on the admission of the patient to the hospital. If the patient has been seen before, the Kahn and the Rh should be known already. That vaginal examination should not be made until all is ready to proceed with the chosen method of delivery is commonly accepted.

Recent papers, as that of Watson and Gusberg, and of Davis and Campbell, incline toward a choice between cesarean section and rupture of the bag of waters, with or without scalp traction by means of the Willett forceps or similar instrument. With this attitude the essayist agrees. The great majority of cases may be managed by one or the other of these two, and the avoidance of the introduction of a foreign body is wise. That the bag is not as yet completely discarded by all clinics is evidenced by the paper of Dr. Seeley before this Society two years ago in which he reported 250 cases of placenta previa in 105 of which the bag had been used. There may still be a place for the bag in an occasional case, but its place is definitely far less than formerly. The vaginal pack I would reject completely; first, because so far as my experience has shown it is inefficient, and, second, because it is dangerous from the standpoint of infection. Such patients as I have seen who have entered the hospital after packing by a physician at home have not caused me to have any confidence in this method.

As to the method of cesarean section, the essayist employs both the classical and the low cervical technique. I believe the latter is definitely the better, and use it in all cases in which abdominal delivery is chosen. I believe it has two advantages. First, should packing be needed, it is far more easily introduced in the lower type of operation; and, second, should there be bleeding from open sinuses in the lower uterine segment, hemostasis by means of actual suture may be employed. This has served me well in a number of instances. In our own work, of the last 45 cases of placenta previa, 21 were delivered by cesarean section. In the entire number there was no maternal death.

Now as to the question of expectancy, I believe that, should the baby be smaller than is compatible with probable continued life after delivery, one may defer interference or await the possible advent of normal labor under advantageous circumstances. By advantageous circumstances I mean that the patient is in a hospital in which there is a well-equipped obstetric service with someone at hand all the time who is able to interfere at once should it be needed. It seems to me that the essayist is extremely bold in allowing these women to go home with instructions to return should repeated bleeding occur. It is true that, as in ectopic pregnancy, few women die from the first bleeding. But no one knows what the second

five babies (12 per cent) were lost. One was a term baby delivered by cesarean section which died neonatally of congenital malformations, and four were prematures, of which one was stillborn and three died neonatally. The fetal mortality of 12 per cent in this group treated expectantly is considerably better than the fetal mortality of 28 per cent for the entire series. In view of the better fetal results and with no apparent increased maternal risk, it would seem that an expectant attitude in the management of placenta previa is worthy of trial.

TABLE V. FETAL RESULTS WITH EXPECTANT TREATMENT

METHOD	NO.	TERM 32		PREMATURE 9	
		LIVED	DIED	LIVED	DIED
Spontaneous	11	9	0	1	1
Rupture of membranes	15	10	0	3	2
Cesarean	15	12	1	1	1
Totals	41	31	1 (3%)	5	4 (44%)
Total Fetal Deaths 5, or 12 per cent					

Summary

One hundred five cases of placenta previa with one maternal death (0.95 per cent) and twenty-nine fetal deaths (28 per cent) are reviewed. The adequate replacement of blood loss, and caution in the use of vaginal manipulations, with delivery either by cesarean section, or induction of labor by rupture of the membranes, dependent upon the station of the presenting part, the degree of previa, and the condition of the cervix, have improved the maternal results in placenta previa. An improvement in the fetal results is dependent upon an attempt to carry these patients closer to term. Of seventy-four babies weighing 2,500 Gm. or more, eight (10 per cent) were lost, while on the other hand, of thirty-one babies weighing less than 2,500 Gm., twenty-one (68 per cent) were lost. An attempt to carry patients with placenta previa to term seems to be reasonably safe and is worthy of trial, although some of them will go into spontaneous labor prematurely, while others will have such persistent or profuse bleeding that one is reluctant to continue an expectant attitude. In forty-one patients so managed, there were five fetal deaths (12 per cent), four prematures, and one term baby which died of congenital defects.

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Discussion

DR. ROBERT KIMBROUGH, JR., Philadelphia, Pa.—Dr. Williams is to be congratulated on the excellent results which he has obtained in the treatment of this series of cases of placenta previa, not only because of his low and unavoidable maternal mortality, but particularly because of the low fetal death rate. I am sorry that Dr. Williams did not have sufficient time to present a table in which he has summarized recent papers on this subject

The number of premature cases in his series, of 20 odd, is approximately 25 per cent. If you deduct those who went spontaneously into labor, there were only relatively few cases to which his proposal to tide the patients over would be applicable. Certainly that possibility must not be overlooked or forgotten. All of us, I am sure, have had specific instances in which that possibility has been exploited with the happiest results. And it is only in that sense, I think, that Dr. Williams is presenting to us a plea for expectancy.

DR. ARTHUR H. BILL, Cleveland, Ohio.—I do not expect to discuss the general treatment of placenta previa, but I think the main point in his paper is that of expectant treatment. I have had some good results from expectant treatment and have saved some babies, and evidently he has also. It is rather characteristic of placenta previa that there will be one hemorrhage, this will stop, and then there will be a recurrence because, as it has been described, the case is one of unavoidable hemorrhage.

I agree with the discussants that if we carry out the expectant treatment we should insist on the patient being in bed and in the hospital during this period of observation. Many years ago there was a patient in the Cleveland City Hospital who had had a moderate hemorrhage, and after a week of no bleeding insisted upon going home because nothing was being done for her. When all arguments had failed, she was permitted to be taken home after signing a release, which absolved the hospital from blame, but did not help the patient. Some days later she was brought back to the hospital in an ambulance with a tremendous hemorrhage, and died in the admitting room before anything could be done for her. If she had remained in the hospital she probably could have been saved. I always insisted, thereafter, that in any case of placenta previa, if the expectant treatment is carried out, the patient should be kept in the hospital and under observation. There are cases where good results may be obtained in this way.

As to the ultimate delivery, prophylactic blood transfusion and classical cesarean section are in order. I prefer classical section because my policy is to keep the uterine incision away from the placental site, for if this is done there will be no post partum bleeding from that source.

DR. WILLIAMS (Closing).—The table which Dr. Kimbrough mentioned was simply a total of the recently reported cases of placenta previa, 1,292 cases with 21 maternal deaths, an average maternal mortality of 1.6 per cent. There were 420 fetal deaths with an average fetal mortality of 32.5 per cent.

I did not mean to give the impression that we advised these patients to leave the hospital. Fourteen of them left the hospital although we would have preferred for them to stay. Fortunately they came back to the hospital with but little bleeding. I would not recommend that the patients with placenta previa leave the hospital unless they lived in close proximity and had easily available means of transportation.

(The remaining papers presented at the meeting will appear in the February issue of the JOURNAL).

hemorrhage may bring, and the fact that one has already taken place means that some unfolding of the lower uterine segment has occurred, and this only increases as time goes on. I believe that expectancy should only be practiced with the patient in a hospital which is so staffed and organized that immediate interference may be begun by a trained individual on the appearance of hemorrhage. I agree with the statement of Adair, made in the discussion of Seeley's paper, "Expectancy or delay is extremely hazardous and if generally adopted would lead to an increased mortality. It should not be carried out except in a special hospital and under expert care." Macafee of Belfast, who is quoted by the essayist, says, "If placenta previa is suspected it is not necessary to keep the patient in a hospital provided she is within a short distance of it." However, he states that this does not apply to multiparas. As these make up the majority of the patients who have placenta previa, his statement is robbed of much of its force.

DR. JOSEPH L. BAER, Chicago, Ill.—At the risk of redundancy I beg to quote a Fellow of this Society, N. Sprout Heaney, to the effect that more patients with ectopic pregnancy die in the hospital while under observation than do those who are treated outside of the hospital. The same applies to placenta previa. Those who are kept under observation indefinitely can eventually sustain major hemorrhage, and before their needs can be met they may sustain exsanguination to the degree that they reach irreversible shock and succumb. I am firmly of the opinion that patients with a diagnosis of placenta previa should not be kept under prolonged observation, but that their pregnancies should be terminated irrespective of the estimated age of the fetus involved.

Concerning the method of termination, I beg to offer a comment concerning rupture of the membranes. Successful rupture of the membranes in the many decades past was confirmed by the demonstration of hair from the scalp of the fetus, and the rupture of the membranes was considered consummated. That, in itself, is totally inadequate for the purpose. It should include drainage of the liquor amnii in order to allow the uterus to contract, and thus to initiate active labor. And so I think it behooves us whenever we speak of rupture of the membranes as a therapeutic procedure in the treatment of marginal placenta previa or for the induction of labor to speak of "rupture and drainage."

DR. SUBODH MITRA, Calcutta, India.—I agree with Dr. Williams' outline of treatment that means no immediate termination of the pregnancy.

I have had a patient near term who had hemorrhaged the day before. There was no bleeding when I saw her so I kept her under observation. In the course of a week's time she had a normal delivery. That case gave me the idea that we should not always follow the beaten track of no temporization in placenta previa. If properly taken care of by hospitalization, we give the patient a better chance to go a little further. Later I treated a number of cases—not all of a serious type—in which I followed that expectant procedure and got good results. So I think it is high time for us to think seriously about whether we should teach this method of expectant management to our students. I think, however, it should not be taught to the students in general.

These patients should never be sent home. In the management of these cases by cesarean section, I have my own way of coming to a decision. It is difficult to know whether it is a case of central or lateral placenta previa unless one makes a thorough examination. I first determine whether the cervix is tubular and undilated, and in that case I advise cesarean section, and that is the only time I do a cesarean section. Otherwise, if the cervix is found taken up and dilatable, one must seriously consider whether it is a case for cesarean section or not.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I think perhaps some of the extent to which Dr. Williams has been misunderstood in his purpose in presenting his cases tonight is due to the unfortunate title. Had he called his paper a plea for expectancy in a few selected cases of placenta previa, the reaction to what he has said would have been more generally favorable.

Department of Reviews and Abstracts

Selected Abstracts

Mammary Glands

Cusmano, L.: Massive Pregnancy Hypertrophy of the Breast, *La Ginecologia* 12: 189, 1946.

True hypertrophy of the breast in which enlargement achieves enormous proportions, and is due particularly to increase of the glandular elements, is a rare event. It is mostly seen during puberty and is quite exceptional during pregnancy. Cusmano reviews the literature on the subject, to which papers of Dellepiane and Aimerich have mainly contributed, and describes a case of massive breast hypertrophy observed in a pregnant woman in the Department of Obstetrics of the Medical School of Parma.

The enormous hypertrophied mammae were quite symmetric, reached the groins of the patient in sitting position, and measured 60 cm. circumference at the base. The skin overlying the mammae appeared stretched, the nipples flattened, the areolae enlarged, reaching a diameter of 9 cm. Tortuosity of the superficial veins was present. The hypertrophic breast gave rise to a dull drag in sensation, and patient was obliged to support that breast during ambulation.

Milk secretion appeared two days after parturition. The flattened nipples made nursing impossible. Treatment was extremely conservative. Compressive bandage of the breast was used. Milk secretion stopped in a few days. The breast regressed to normal size in three months. Patient had previously shown in two former pregnancies moderate hypertrophy of the breast which, however, did not interfere with normal nursing.

GEMMA BAEZILAL

Malignancies

Cusmano, L.: Carcinoma of Cervix, Follow-Up Study of 281 Cases, *La Ginecologia* 8: 249, 1946.

L. Cusmano of the Gynecological Department of the Medical School in Parma reports statistical results in 281 cases of carcinoma of the cervix treated in the institute over a period covering ten years (1933 to 1944), and representing 3.6 per cent of the 7,666 gynecologic patients seen during this period. Age incidence in this group showed the presence of three cases under 30 years of age (1.06 per cent), of 39 cases between 30 and 40 years of age (13.78 per cent), 212 cases between 41 and 65 years of age (75.4 per cent), 27 over 60 years of age (9.6 per cent). Highest incidence in this group coincides with the average age incidence of carcinoma of the cervix. Carcinoma of the cervix in young women, however, appears to be exceedingly rare in the material observed in Parma. There were but 17 nulliparous women in the whole group, and the proportion of multiparous women is definitely higher than observed in average surveys. Multiparous women, however, distinctly predominate in Parma: women having more than five children reaching 49 per cent of the entire group observed in the Gynecological Department. No conclusion can therefore be drawn as to correlation between number of pregnancies and aptitude to develop cancer. It is noteworthy, however, that among the 281 cancer cases pluriparous women average a higher age in the development of cancer. Multiparous women with more

Editorial

An International Congress on Obstetrics and Gynecology

In a previous editorial (November, 1947), we commented upon the desirability and importance of holding an international congress devoted to this important field of medicine. It is of interest to report that the Board of Directors of the American Committee on Maternal Welfare have agreed to sponsor such a conference in conjunction with the Fourth American Congress, and it was decided to hold it in New York City at the Hotel Pennsylvania, May 14 to 19, 1950. The place of meeting is the metropolis of the Western world, and is readily accessible by accepted modes of travel from all parts of the globe.

Preliminary plans include a program in which each morning of the four-day scientific sessions is to be devoted to formal presentation and discussion of a general topic. The afternoon sessions are to be given over to round table and informal discussions of these subjects. Tentatively selected are cancer of the female genitals, physiology and pathology of reproduction, and gynecologic procedures.

The field of obstetrics and gynecology involves wide implications, therefore it is important to include all interested groups—doctors, nurses, hospital administrators, public health personnel, and medical educators. An additional session at the close of the conference may be devoted to a presentation of economic and sociologic problems under the auspices of the National Federation of Obstetric-Gynecologic Societies.

In addition to the academic presentations to be made at the Congress there will be extensive technical and scientific exhibits, as well as social events. There will be opportunities for the participants from foreign countries to mingle with each other, peacefully to discuss their problems, and to become acquainted. There is nothing more likely to develop progress and interest in the advance of the speciality than such harmonious personal contacts. In conjunction with the Congress, it is likewise planned to develop clinics in various of the larger medical centers and hospitals of the country both before and afterwards, so that foreign visitors will have an opportunity to acquaint themselves with the advances of American institutions in this field.

Further details of the various activities will be announced as soon as plans are developed.

The executive offices of the Congress are located at 24 West Ohio Street, Chicago 10, Illinois, U. S. A., and all inquiries should be addressed to the General Chairman, Dr. Fred L. Adair.

The American profession is pleased to welcome the visitors to what is looked forward to as an unequalled opportunity for the advance of this important branch of medicine, for the commingling of people inspired by the same endeavors can only bespeak progress in a subject of global interest. For women-kind, healthy and well, means world-wide happiness.

considered inoperable, whereas all of the cases of carcinoma of the body could be operated upon. The cases of cervical carcinoma are graded by Bianchi according to the League of Nations' classification, and five-year end-results are as follows: in stages 1 and 2, in the group treated by surgery alone, a cure rate of 77 per cent was reached; in all groups that received surgical treatment plus irradiation a 100 per cent cure rate was attained. In the group treated by combined radium and x-ray irradiation the five-year cure rate was 85 per cent.

In cases belonging to stage 3, a 20 per cent cure rate was observed after surgical treatment followed by irradiation, and a 28 per cent rate in cases treated by combined radium and x-ray therapy. In group 4, no five-year cure was noted. Average five-year cure rate was 41.8 per cent. Cancer of the body was cured in 100 per cent of the cases. Primary surgical mortality was 9.3 per cent. This study confirms that patients of stage 3 are best treated by x-ray, patients of stages 1 and 2 by surgery. The Wertheim's panhysterectomy was used in most of the cases.

GEMMA BARZILAI.

Cesarean Section

Gray, T. Cecil: d-Tubocurarine in Cesarean Section, *Brit. M. J.* 4500: 444-445, 1947.

Gray, of the Whiston County Hospital, reports on his experience using d-tubocurarine as an inductant for cesarean section in 30 cases. Atropine, 0.65 mg., was given one hour preoperatively; followed by d-tubocurarine, 15.0 mg. injection; while some "kemithal" (cyclohexenyl-allyl-thiobarbiturate) 0.3 Gm. in 5.0 per cent solution, as an injection, followed the d-tubocurarine and anesthesia was subsequently maintained by cyclopropane.

All the infants, save two, cried lustily upon birth. The author observed an increased contractility of uterine muscle permitting him to omit usual postpartum "pituirine."

Because of the extremely light anesthesia the patients usually awakened, with rare postoperative retching or vomiting, as the dressings were applied. On occasion he did note slight residual signs of curarization at the end of an unusually quick operation, but only on two occasions was it necessary to utilize the antidotes "prostigium" and atropine. There was no urinary retention, ileus or eye symptoms in this series. Gray finds d-tubocurarine safe and valuable primarily in that its use prevented a long postoperative depression.

C. E. FOISOME.

Peralta, Ramos A.: Abdominal Drainage in Unclean Cases of Cesarean Section, *Obst. y ginec. Latino-Am.* 4: 715-728, 1946.

The maternal mortality in unclean cases of cesarean section is still very high. Drainage such as is employed after the low, cervical operation is either useless or harmful, but drainage in cases of extraperitoneal cesarean section is effective and hemostatic. Our hope of reducing the death rate lies in the use of the antibiotics. However, the application of antibiotics in infected cases does not mean that we can discard the Porro operation, the extraperitoneal operation, nor drainage in selected cases. The author agrees with Sterling Mueller that the advice concerning appendicitis—namely: "In doubtful cases drain"—is as valid today as it was before the introduction of the sulfonamides.

J. P. GREENHILL.

Neme, B., and Esteves, J.: The Problem of Anesthesia in Cesarean Operations, *An. Brasil de ginec.* 22: 174-185, 1946.

The authors analyzed the type of anesthesia used for 559 cesarean sections performed at the University of San Paulo. The incidence of the different types was as follows: spinal 74.9 per cent, inhalation 16.8 per cent, peridural 2.9 per cent, sacral 0.5 per cent, and intravenous 0.3 per cent. For subarachnoid block, hypertonic senrocaine solution was used in 95.7 per cent of the cases, and for the inhalation anesthetics ether and balsalform were

than nine children developed cancer at an average of 60 years, while nulliparas, uniparas and multiparas with less than five children showed cancer development at an average age of 50 years. In 11 per cent of the observed cases, other cases of cancer were present in the family, and in 4.3 per cent cervix carcinoma had been present in the mother. Nineteen and nine-tenths per cent of the cases observed in this group belonged to stage 1, 28.8 per cent to stage 2, 35 to stage 3, and 47 to stage 4. One hundred thirty-seven cases, i.e., 48 per cent of the whole group, were operable, 97, i.e., 34 per cent, were inoperable, and 47 were advanced cases. Eighty-five per cent of the cases in the group were treated by surgery, 125 by radium therapy, 59 by surgery and radiation therapy, 12 cases (incurable cases) received symptomatic therapy only. Five-year cures in cases treated through 1940 were observed in 55.3 per cent of cases treated by Wertheim method (throughout stage 1 or 2 cases), in 78 per cent of cases treated by total hysterectomy and followed by deep radiation therapy, and in 48 per cent of the cases treated by vaginal operation. Cases treated with radium therapy (including 65 per cent of stages 3 and 4) showed five-year cure in 33 per cent of the cases. Furthermore, of four cases of stump carcinoma, three were alive after five years. In this group, therefore, the best results were attained by total hysterectomy followed by deep x-ray therapy.

GEMMA BARZILAI.

Rocha, A. H.: Colposcopy in the Early Diagnosis of Cervical Cancer, *Obst. y Ginec. Latino-Am.* 4: 728-749, 1946.

In a series of 800 women whose cervixes were examined by means of the colposcope, the author found seven cases of early cancer. All of these patients came for gynecologic conditions other than for disturbances of the cervix. One woman was pregnant, one had prolapse of the uterus, three had syphilis and one had stenosing lymphogranulomatous proctitis. In all of the seven cases of cancer discovered by means of the colposcope, the diagnosis was verified by histologic examination. In addition to the seven cases of early carcinoma there were twenty-three cases of advanced cancer easily detectable without the colposcope. The author advocates amputation of the cervix in all cases where the cervix presents atypical epithelium. He further advises the use of the colposcope before every biopsy and every electrocoagulation of the cervix.

J. P. GREENHILL.

Campbell, James V., and Singman, David: Primary Ovarian Malignancy, *West. J. Surg.* 55: 263, 1947.

From the Highland Alameda County Hospital comes a report on 69 cases of primary ovarian malignancy. Most cases occurred in women past 60 years of age (24 per cent) and relatively few cases (12 per cent) under 40 years of age. The youngest was a dysgerminoma in a girl, aged 12 years. One case of arrhenoblastoma was seen in a girl, aged 14 years. The great majority fell into the class of papillary serous cystadenocarcinoma. There was an over-all five-year survival of 14 per cent (8 per cent for 46 malignant cystic tumors, 30 per cent for 10 solid tumors, and 100 per cent for three functional tumors). Several factors influence the prognosis: ascites, metastases, bilateral involvement, and the degree of cellular anaplasia. It was impossible to evaluate the value of x-ray therapy. Some patients apparently benefit from it. In others its use is followed by no consistent effects. Since the disease is one most commonly affecting the senile ovary, the question is posed, "Should all menopausal or postmenopausal enlargements or tumors of the ovary be removed, irrespective of size or symptoms?"

WILLIAM BICKERS.

Bianchi, P.: Carcinoma of Cervix and Corpus Uteri in Young Women, *Riv. d' Obstet. e Ginec.* 1: 113, 1946.

In young women under 35 years of age, P. Bianchi of the Gynecological Department of the University of Florence collected during the years 1922 to 1941 76 cases of carcinoma of the cervix uteri, and 11 cases of carcinoma of the body. In most of the cases, early symptoms had been neglected, and 49 of the 76 carcinomas of the cervix uteri were

Endometriosis

da Costa, C. C.: *Extragenital Localization of Endometriosis*, *Obst. y Ginec. Latino-Am.* 4: 387-409, 1946.

The author reports two cases of extragenital endometriosis situated in an umbilical scar. The first followed a cesarean section, and the other was associated with an adenomyoma of the round ligament. At the author's clinic during the last ten years, there were 33 cases of endometriosis among 2,285 operations (1.44 per cent). The distribution was as follows: tube 10, ovary 8, fibromyoma of the uterus 7, uterine corpus 3, round ligament 2, umbilical scar 2, and laparotomy scar 1. In the Brazilian literature he found reports of 24 cases of endometriosis of all types.

J. P. GREENHILL.

Fallon, John, Brosnan, James T., and Moran, William G.: *Endometriosis*, *New England J. Med.* 235: 669, 1946.

The authors discuss the etiology, symptoms, and treatment of endometriosis. They are of the opinion that endometriosis is an antivenereal disease—that is, it is associated with sexual unfulfillment. The prophylaxis seems to be early marriage and a child every few years.

Because endometriosis can be seen long before it can be felt, the practitioner should be as radical about advising early surgical exploration, and extirpation of all new growths of endometrial tissue, as the surgeon is conservative about castration.

JAMES P. MARR.

Macleod, Douglas: *Endometriosis: A Surgical Problem*, *Brit. J. Surg.* 34: 8, 1946.

The author deals mainly with extragenital endometriosis. The various theories of endometriosis are reviewed. Some of the more common manifestations of the disease are discussed. Various extragenital organs are reviewed, such as the perineum, umbilicus, bladder, ureter, laparotomy scar, bowel, small intestine, sigmoid, colon, and rectum. The author stresses the importance and difficulty of differentiating endometriosis of the rectum from malignancy. From a survey of all of the facts, it appears that endometriomas, wherever they occur, are the result of the endometrium taking upon itself lymphatic permeation. It is felt that endometriosis must be accorded a position somewhere between benign and malignant growths.

WILLIAM BERMAN.

Abell, Irvin, and Abell, Irvin, Jr.: *Endometriosis*, *South. Surg.* 13: 321, 1947.

There is no classical, clinical symptoms or physical findings which will consistently lead one to the correct diagnosis of endometriosis. It may mimic almost any other pelvic lesion, and occurs in association with other forms of pelvic pathology, even develops in company with carcinoma. Lesions of endometriosis have been found in all the pelvic organs, the inguinal region, abdominal wall, and at points distant from the pelvis, such as the lung. However, it shows a decided preference for the ovary, and in the series of cases here reported forced surgical castration in 60 per cent of the cases.

There are two theories of etiology, namely: (1) heteroplasia of tissue arising from coelomic epithelium; and (2) implantation theory of Sampson.

In support of the heteroplastic theory and in criticism of the implantation theory, the authors note that regurgitation of menstrual blood through the Fallopian tubes is never seen while operating upon women during menstruation and, furthermore, the endometrial tissue desquamated at menstruation is nonviable and, therefore, not capable of transplantation. Treatment cannot be generalized, but must be individualized on the basis of the patient's age, desire for children, and extent and location of the pathology.

WILLIAM BICKERS.

employed in 90.3 per cent of the cases. At the present time, cyclopropane gas-ether is preferred. The authors believe that hemorrhage is an important cause of death in cesarean section, and this complication is high after inhalation anesthesia. Peridural, local, and spinal anesthesia have a low incidence of hemorrhage.

A higher percentage of babies delivered under inhalation anesthesia required resuscitation than those delivered under spinal anesthesia. In order to reduce the death rate of 0.7 per cent and the incidence of hypotensive states of 2.3 per cent, spinal anesthesia should be administered only by trained anesthetists. Complementary anesthesia was necessary in 6.9 per cent of the spinal cases, 15.3 per cent of the peridural cases, 31.2 per cent of the local series, and 100 per cent of the intravenous group. The authors believe there are dangers of spinal anesthesia, but they no longer use this anesthetic in hypertension cases, and never with abruptio placentae.

J. P. GREENHILL.

Aguilo, A. J.: Peritoneal Sulfonamide Therapy During Cesarean Section at the San Borja Maternity, Bol. Soc. Chilean de Obstet. y Ginec. 11: 39-55, 1946.

According to the author, the prophylactic use of the sulfonamides during uterine cesarean sections is a great advance. In a series of 54 uterine cesarean sections in which the sulfonamides were used intraperitoneally, there were no deaths from peritonitis. The total death rate from peritonitis decreased to 1 per cent. Hence more women may be permitted a thorough test of labor than hitherto, and cesarean section may be performed with safety. The addition of penicillin after operation improves still further, the good results obtained with the intraperitoneal use of the sulfonamides. However, the benefits derived from these drugs should not lead to errors in technique and carelessness. In the author's clinic the highest maternal mortality in the cesarean section cases is from shock and acute anemia, the result of total placenta previa (3 per cent).

J. P. GREENHILL.

Endocrinology

Price, Dorothy: The Influence of Maternal Hormones on the Reproductive Organs of Suckling Rats, Anat. Rec. 97: 519-545, 1947.

Price, of the University of Chicago, in the Hull Zoological Laboratory, in a well-documented article, exhibits evidence that ovarian androgens of lactating female albino rats reach the suckling young in effective amounts via the milk, and contribute in some degree to the growth of the male prostate and seminal vesicles.

The significance of the findings that maternal hormone stimulates growth in the reproductive tract of the suckling young rat lies in the fact that it proves that suckling animals have access to hormones from sources other than their own endocrine glands.

The author concludes further that there is no evidence from this study that estrogens from the mother have any effect upon the organs of suckling male or female albino rats.

C. E. FOLSOME.

Szarka, Von Alexander: The Pseudo-Pregnancy Picture Induced by Massive Doses of Follicular and Corpus Luteum Hormones, Gynaecologia 122: 338-346, 1946.

Szarka, of the Second Woman's Clinic of Budapest University, administered to an oophorectomized woman 4,000,000 international units of follicular hormone and 400 mg. of crystalline progesterone. He was able to induce experimentally decidual-like changes similar to those seen in early pregnancy. He checked his observations both clinically and by endometrial study. He concludes his article with a discussion about several minor histologic points of difference in this specimen and those of early pregnancy, and attempts to correlate these details to the quantitative and chronological conditions of the two hormones.

C. E. FOLSOME.

Reply by Dr. O'Connor

To the Editor:

It is true that Father Ford did not see my paper as finished. He was in Rome at that time, and, because of this and because I thought I understood his position and because I thought the further development was purely clinical, I did not contact Father Ford about the article as finished. I wish to state clearly now that I do not propose hysterectomy in any case as a more satisfactory method of sterilization than tubal resection. I am opposed to any form of sterilization which has as its purpose sterilization as such. As I go over my article again with Father Ford's statements before me, I believe that the impression could be obtained that one of my purposes in recommending cesarean hysterectomy was because it removed remote dangers, but my interest from the beginning was the relative immediate mortality of cesarean hysterectomy and the conservative operation. As I studied this subject more I became convinced of the immediate safety of the former. This conviction has been strengthened by the clinical results of Drs. Reis and deCosta whose paper appeared in the *J. A. M. A.*, vol. 134, June 28, 1947, and who believe that the mortality of cesarean hysterectomy is not any more than that of any supracervical hysterectomy and this, of course, is 0.5 per cent or less. I think that I may have created confusion in the minds of some Catholic doctors by mentioning on more than one occasion the remote aspects and the future welfare of the patient, but my prime and main interest and object was to stress the immediate safety of this operation in comparison with other procedures. Father Ford's statement of the moral aspects is acceptable to me and, indeed, welcomed because it will clarify both his position and mine. I understand that his position is tentative and hypothetical. The main purpose of the operation I recommended is that I believe the medical indications for cesarean hysterectomy in some cases should be extended, as I believe that the operation will be found to be much safer immediately, here and now, than the conservative operation. Every case, as Father Ford stressed, must be individualized, and the immediate safety of the patient is the controlling consideration. I have not in the past and do not now recommend any operation whose purpose is contraceptive.

CORNELIUS T. O'CONNOR, M.D.

BOSTON, MASS.
Sept. 17, 1947

Retroversion of the Uterus

To the Editor:

I have just read Dr. Carl T. Javert's and Dr. H. B. Atlee's letters in the May JOURNAL discussing retroversion of the uterus as an etiological factor in abortion, nausea of pregnancy, backache, and sterility. Dr. Atlee decries the teaching of many, if not most textbooks, that retroversion is an important cause of these conditions. He, apparently, bases his opinion that it is not, on his clinical experience. Indeed, what other basis is there on which an opinion can be based? Dr. Javert upholds the opposite view. He buttresses his opinion by quoting as authorities two well-known writers. Neither Dr. Javert or these two writers seem to base their opinions on anything more substantial than the fact that they are "the accepted opinions of American authorities."

Several years ago, after twenty-four years of active practice, fourteen of them as a specialist in gynecology and obstetrics and visiting obstetrician on the staff of a large obstetric hospital and a large gynecologic service, I began to suspect that retroversion of the uterus was not a frequent cause of miscarriage. I consulted ten standard works. The weight of opinion was that retroversion is an important cause of miscarriage, but individual opinions varied from "retroversion is a not uncommon cause of abortion" to "the danger of abortion is not much greater than in the normal individual unless the uterus is adherent or becomes impacted in the pelvis." (As to impaction, a few words later.) Not one of the writers consulted gave any statistical data to support his opinions. It was my impression that most of these authorities, as did Dr. Javert, relied not on clinical data but on "authority;" that

Correspondence

The Repeat Cesarean

To the Editor:

In the *American Journal of Obstetrics and Gynecology*, vol. 53, p. 914-926, June, 1947, an article written by Dr. C. T. O'Connor appeared regarding the risk involved in repeat cesarean section. Dr. O'Connor recommends the removal of the uterus in certain cases in order to lessen the risk to the mother. He quoted in part an article of mine in *Theological Studies*, December, 1944, vol. 5, p. 514 ff. The impression conveyed is that my remarks in *Theological Studies* are the basis for the moral aspects of his paper. This impression that I would approve of the conclusions as they appear in his paper is not warranted—and for two very important reasons: (1) I did not see Dr. O'Connor's paper as finished. (2) The case he now proposes appears to me to differ in at least one crucial point from the case I discussed in *Theological Studies*. The operation, if I read Dr. O'Connor's paper aright, is intended partially to prevent future dangerous conceptions. In fact, if I were not aware of his long record of service in Boston, and particularly in St. Elizabeth's Hospital, I would conclude from Dr. O'Connor's article that he was proposing hysterectomy in these cases as a more satisfactory method of sterilization than tubal resection.

In order to remove a source of confusion and error let me state my position.

Direct sterilization is forbidden; that is, sterilization chosen for its own sake, or chosen as a means of preventing dangerous conceptions. Operations which merely *result* in sterility are sometimes permitted on certain conditions; for example, first, that the resultant sterility is not chosen either as an end in itself or as a means to the patient's health, and secondly, that there exists a proportionately grave cause for permitting so grave a mutilation. Accordingly, I tentatively approved of hysterectomy in certain repeat cesareans on condition that the object of the operation was to safeguard the patient's health here and now, and not to safeguard it by preventing future dangerous conceptions, and on condition that sufficiently grave reasons existed for permitting the destruction of so important a function. This second condition was fulfilled *if* the clinical conclusions were correct, namely, that the radical procedure (cesarean hysterectomy) not only brought about a much smoother convalescence, but reduced by one-half the danger of death to the mother from the simple cesarean and its immediate consequences. And I gave this opinion in the further supposition that the case involved a repeat cesarean, and that the patient owed maternal duties to her living children. A reduction of mortality from 2 per cent to 1 per cent, or from 1.5 per cent to 0.5 per cent would be a very significant and important difference from a moralist's as well as from a surgeon's viewpoint, and would mean that the operation was at least twice as safe for the mother here and now. All these reasons seemed to me sufficient to permit, with the patient's consent, the resulting sterility.

My opinion was tentative, in that I wanted to hear what other moralists had to say before coming to a definite conclusion. So far, I have seen no arguments that would induce me to change my mind.

And my opinion was hypothetical and still is. For it is based on the hypothesis that Dr. O'Connor's clinical conclusions are established for practical purposes. Naturally, I am not the judge in these clinical matters.

I wish Dr. O'Connor would reassure me as to the purpose of the operation he recommends in his paper, for as it stands at present I cannot approve of it, and I do not feel that any Catholic moral theologian would.

JOHN C. FORD, S.J.
Professor of Moral Theology
Weston College

Sept. 15, 1947

Necrology

JAMES R. GOODALL, M.D., of Montreal, professor of obstetrics and gynecology at McGill University since 1912, recipient of many honorary degrees, participant in World War I as a medical officer, a frequent contributor to American and English journals, well known for his work on endometriosis, died suddenly on Sept. 25, 1947, at the age of 77 years.

ROBERT MEYER, M.D., notable embryologist and gynecologic pathologist, a field in which he pioneered in all of its branches, migrating to this country from his native Germany during the Hitler regime and settling in Minneapolis as a member of the staff of the University, died there on Dec. 13, 1947, at the age of 84 years. A prodigious scientific output included his monumental work on the embryology of the vagina and various fetal anomalies, his studies on ovarian tumors, on the life cycle of the corpus luteum, the correlation of the ovarian and endometrial cycles, many contributions to the knowledge of genital cancer, as well as hydatidiform mole and chorionepithelioma.

CURTIS F. BURNHAM, M.D., of Baltimore, long associated with the Kelly Clinic, and prominent in the development of radiotherapeutic procedures in gynecology, associate professor at Johns Hopkins, born in Richmond, Kentucky, Jan. 17, 1877, died in Baltimore, Dec. 17, 1947, at the age of 70 years.

Item

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 16-22, 1948, in Washington, D. C. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pa.

PAUL TITUS, M.D.

the belief that retroversion of the pregnant uterus is a condition dangerous to either the fetus or the mother is a superstition passed on from one generation of medical men to another in the textbooks, without the verification of clinical observation.

About twenty years ago, for my own satisfaction and as a basis for an unpublished paper read before a small local medical club, 674 consecutive obstetric cases in the practice of my partner (the late Bertram H. Buxton) and myself were analyzed. Of these 674 cases, 325 were examined before the fourth month, by which time the retroverted pregnant uterus has either risen out of the pelvis or become incarcerated.

Among these 325 cases examined before the fourth month, the uterus was found to be in normal position in 271 (83 $\frac{1}{3}$ per cent), and in retroversion in 54 cases (16 $\frac{2}{3}$ per cent). Among the 271 cases with the uterus in normal position, there were 37 miscarriages or abortions (13.6 per cent).

Among the 54 cases with retroversion, there were six miscarriages or abortions (11.6 per cent).

The incidence of abortions and miscarriages was higher among the normal cases than among those with retroversion.

Thus my suspicion that, in our private practice at least, retroversion of the uterus was not a great threat to fetus or mother, was proved to be justified. None of these cases became incarcerated. Dr. Atlee has seen only one incarcerated uterus in approximately 4,000 cases. My experience coincides with that of Dr. Atlee. In forty years of an active obstetric practice, I can recall only three cases of incarceration of the pregnant uterus—none of them in my own patients, but seen in consultation with other men. I suspect that Dr. Atlee and I do not mean by "incarceration" the same condition as does Dr. Javert. The uterus truthfully cannot be said to be imprisoned in the pelvis until after the fourth month—the door of the pelvic prison is wide open up to the time the uterus has reached such a size that it cannot rise above the promontory of the sacrum or be replaced by manipulation from below. I suspect that if a three months' pregnant retroverted uterus was replaced with or without anesthesia because of backache and other pressure symptoms, Dr. Javert would consider it a case of incarceration; that probably Dr. Atlee would not. I certainly would not. I can account for the divergence in the experience of Dr. Atlee and that of Dr. Javert only on a basis of a confusion in terms or possibly that Dr. Atlee gives a retroverted uterus a chance to escape from its pelvic prison more often than does Dr. Javert.

From a series of cases so small as the one here reported no definitive conclusions can be drawn. Furthermore, it is impossible to know how many patients miscarry before consulting a doctor. However, this series would seem to indicate that when at the first examination a pregnant uterus is found to be retroverted, there is no cause to be alarmed. For many years I have made no effort to replace a retroverted pregnant uterus except to demonstrate to the patient how to assume the knee-chest position and, in symptomless cases, often not even that. The results have been just as satisfactory as when the uterus was replaced and a pessary inserted.

EDWARD S. BRACKETT, M.D.

PROVIDENCE 6, R. I.
August 29, 1947

- Texas Association of Obstetricians and Gynecologists. (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists. (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists. *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society. *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society. (1941) *President*, Carl M. Helwig. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society. (1942) *Secretary*, Emmett A. Mechlér, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology. (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society. (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology. (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society. (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society. (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society. (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society. (1924) *President*, George Muscillo. *Secretary*, Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society. (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society. (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society. (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society. (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada. (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society. (1946) *President*, L. L. Bottsford. *Secretary-Treasurer*, N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology. *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society. (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society. (1947) *President*, M. E. Grier. *Secretary*, B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society. (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society. (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society. (1947) *President*, Samuel A. Cosgrove. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society. (1947) *President*, Colin C. McCorriston. *Secretary-Treasurer*, K. S. Tom, 296-E South Vineyard Street, Honolulu 39, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. (1876) *President*, Emil Novak, Baltimore, Md. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be held at Williamsburg, Va., May 24, 25, and 26, 1948.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists. (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists. (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society. (1863) *President*, Albert H. Aldridge. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. (1878) *President*, Aaron E. Kanter. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society. (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, W. O. Johnson. *Secretary*, W. E. Oldham, 842 Barrett Avenue, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. (1934) *President*, Joseph A. Hepp. *Secretary*, Clarence H. Ingram, Jr., 6004 Penn Avenue, Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. (1861) *President*, Frederick J. Lynch. *Secretary*, Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society. (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society. (1933) *President*, Lawrence Lee Cockerille. *Secretary*, Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society. (1924) *President*, Dr. Earl Conway Smith. *Secretary*, John S. Herring, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society. (1924) *President*, Joseph A. Hardy, Jr. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society. (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

Keith, and Rowntree.² But their supply of dye was cut off by World War I, and they were able to make determinations on only thirteen patients anywhere from two to sixty-one days before labor, and on eleven of these women from one to eleven days post partum. In each instance there was a post-partum decrease in TBV, but not invariably when calculated per kilogram of body weight. Their data show enormous variations in TBV both before delivery (range, 3 to 7 liters) and afterwards (2.5 to 5 liters). The more recent experience with the Keith-Rowntree method in 100 attempted observations at the Boston Lying-in Hospital³ makes one question the validity of Miller's figures.

In 1934, Dieckmann and Wegner⁴ published the results of a much more extensive blood volume study. They employed the method of Keith and Rowntree, but substituted Congo red for vital red because some of their subjects were seriously discolored by vital red. Their conclusions were: (1) TBV and PV begin to increase in the first trimester, with gains of 16 and 18 per cent, respectively, "by the thirteenth week;"⁵ (2) the *average* increase at term is 23 per cent for TBV and 25 per cent for PV; (3) by eight weeks post partum the average decrease is 16 per cent for both TBV and PV. These values were calculated by a peculiar mathematical manipulation which involved the assumption that the first antepartum value obtained for any subject represented the true base line for that individual. All subsequent values were divided by this initial figure, the quotient being multiplied by 100 to compute percentage of change. Similarly, the post partum changes were computed by using the value obtained at term as a divisor. Thus, the 23 per cent increase in TBV represented the *average* increase for fourteen patients, but it should be pointed out that two subjects actually exhibited a *decrease*, and two showed "no change" (a variation of less than 5 per cent). Their table in which post-partum changes are summarized shows an *average decrease* in the early puerperium of 13.5 per cent, yet it appears from the detailed data for the various subjects that seven of thirteen women had a *greater* TBV one or two weeks after delivery than they did at term. Because of these inconsistencies we computed standard errors for Dieckmann and Wegner's data, and compared differences between the means of their values at various stages of gestation. The results are shown in Table I. The

TABLE I. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. AT VARIOUS TIMES ANTE PARTUM AND POST PARTUM, CALCULATED FROM DATA OF DIECKMANN AND WEGNER

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R*	P	SIGNIFICANT DIFFERENCE
12-20 wks. : 36-40 wks.	800	390	2.05	0.0404	?
12-20 wks. : 2 wks. pp.	655	387	1.69	0.0910	No
12-20 wks. : 8 wks. pp.	102	465	0.21	0.8337	No
36-40 wks. : 2 wks. pp.	145	325	0.45	0.6527	No
36-40 wks. : 8 wks. pp.	902	415	2.17	0.0300	?
2 wks. pp. : 8 wks. pp.	757	412	1.83	0.0672	No

*R is the ratio of difference to its standard error.

†This statement apparently is in error and it seems likely that the authors meant to say "by the thirtieth week," since their Table 8 shows average increases for the period 26-35 weeks amounting to 15.8 per cent for TBV and 18.2 per cent for PV.

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(Continued from the January issue)

BLOOD VOLUME IN PREGNANCY*

A Critical Review and Preliminary Report of Results With a New Technique

CHAS. E. McLENNAN, M.D.,† AND L. G. THOUIN, M.D., SALT LAKE CITY, UTAH
(From the Department of Obstetrics and Gynecology, University of Utah School of Medicine)

FROM time to time and for various reasons investigators have interested themselves in the question of what happens to the volume of the blood during pregnancy. With the passage of years new and presumably better techniques for the determination of blood volume have become available and have been applied to the problem. Thus, as might be expected, no two studies have been carried out by exactly the same technique, and each author, in turn, has questioned the validity of previously reported results. Despite the fairly general acceptance of the notion that there is a real increase in volume of plasma and red cells‡ during pregnancy, there is no agreement as to the precise magnitude of this increase at the various stages of gestation or the rapidity with which the volumes return to normal in the postpartum period. The possibility that the dye-dilution method for plasma volume might be subject to a sizable error owing to dye which passes to the fetal circulation, or which is merely trapped in the placenta, has been considered, but apparently never very extensively. The advent of still another modification of the dye-dilution method, designed to eliminate some of the errors inherent in earlier techniques, suggested to us the desirability of reopening the question of blood volume in pregnancy to see whether divergent viewpoints now recorded in the literature might be clarified.

Soon after the development in 1915 of the Keith-Rowntree method¹ for plasma volume, using vital red, it was applied to pregnant women by Miller,

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†Present address: Stanford University Hospital, San Francisco, Calif.

‡Throughout this paper PV = plasma volume, TBV = total blood volume, and RCV = red cell volume.

ninth lunar month amounting to 46 per cent and 17 per cent, respectively. These investigators concluded that there is a progressive increase in PV and TBV beginning early in pregnancy, reaching a maximum in the ninth lunar month, with a "definite decrease" beginning during the tenth month and a rapid decline to normal values by the end of the second postpartum week.

Closer scrutiny of Thomson's³ original data reveals that the maximum values shown at the ninth lunar month represent averages of determinations made on only eight women, and that some of the other average values are based on as few as four or five individual determinations. When standard errors are computed for the various means, and significance of differences determined, it is seen that the peak value for TBV is *not* significantly different from the somewhat lower average value found in the tenth month. Indeed, there is considerable doubt that the mean value shown for the fifth ante-partum month is really significantly different from the value at term. On the other hand, there appears to be no question as to the reality of the difference between the nonpregnant value for TBV and that found at term in the pregnant women (Table II, Fig. 1).

TABLE II. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. FOR NONPREGNANT CONTROLS AND PREGNANT WOMEN AT VARIOUS STAGES OF GESTATION, CALCULATED FROM DATA OF THOMSON, HIRSHEIMER, GIBSON AND EVANS

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R	P	SIGNIFICANT DIFFERENCE
5 mos. ante partum : term	710	339	2.10	0.0357	?
9 mos. ante partum : term	508	371	1.37	0.1700	No
5 mos. ante partum : 9 mos.	1218	358	3.40	0.0007	Yes
Controls : term pregnant	1365	265	5.15	0.0001	Yes

Very recently there appeared the study by Roseoe and Donaldson⁸ in Edinburgh. This paper was published after our work was started, but since it did little to clarify the issues, we thought it worth while to proceed as planned. Roseoe and Donaldson used the technique for Evans blue which was described by Davis,⁹ and which involves taking only a single sample of dyed plasma ten minutes after injection of the solution of Evans blue. Their values for blood volume were expressed as milliliter per square meter of surface area, although they pointed out that the formula used to compute area probably did not give the actual surface area in a pregnant woman. The fallacy of assuming in pregnancy a correlation between blood volume and weight of subject (surface area being related to weight) was pointed out by previous writers.^{3, 4} Twenty women at three different stages of pregnancy were used as subjects, and twenty normal nonpregnant women served as controls. Taken individually, the results were somewhat erratic, in that some patients exhibited a drop in volume between the twelfth and twenty-fourth week of pregnancy, while others showed a drop between the twenty-fourth and thirty-sixth weeks. But the mean values for the three periods demonstrated a steady upward trend for TBV from 4,300 c.c. at twelve weeks to 5,400 c.c. at thirty-six weeks, or an increase of about 25 per cent in absolute volume. Expressed in terms of surface area the increase

thirteen subjects in their "Series A," studied at 9 to 20 weeks ante partum, at term (36 to 40 weeks), 11 to 14 days post partum, and eight weeks post partum showed mean values which were not significantly different at any of these times, unless one chooses to claim that an R value of just over 2.0 denotes a difference of real significance. Looking at the data in this light would suggest either that blood volume does not change significantly during pregnancy and the puerperium, or that the method employed in the study was unreliable.

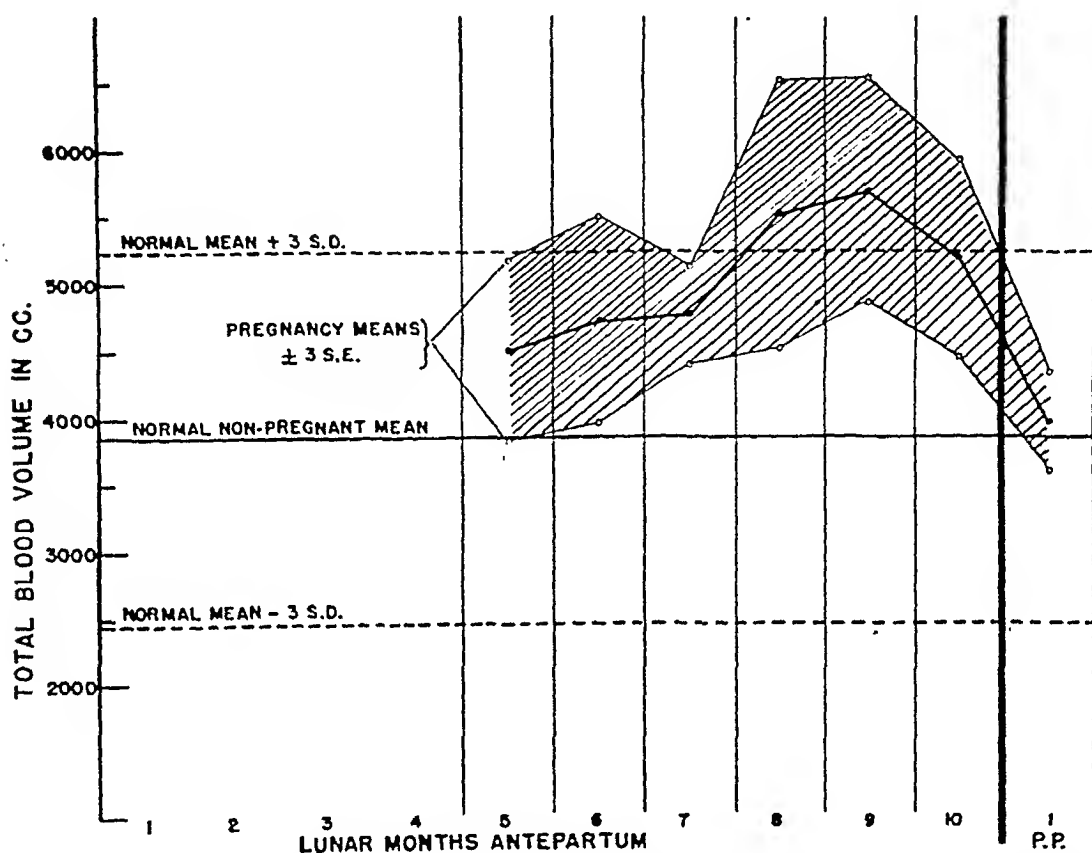


Fig. 1.—Curve of mean total blood volume during pregnancy, from data and chart of Thomson and associates, redrawn to indicate limits of mean ± 3 standard errors (cross-hatched area). Note that the mean value for the ninth month falls well within the range of mean ± 3 standard error for the tenth month, indicating that the difference is not significant. Similarly, the difference between mean values at five and ten months is of questionable significance.

The next careful study of blood volume in normal pregnant women was reported by Thomson, Hirsheimer, Gibson, and Evans in 1938.³ Using the azo dye Evans blue (T-1824) and the method of Gregersen, Gibson, and Stead,⁵ as modified for clinical use,⁶ they made determinations on fourteen women at various times throughout pregnancy and the puerperium, and compared the results with values for a group of twenty-eight normal nonpregnant women included in the study of Gibson and Evans.⁷ Their values for pregnant women were grouped according to lunar month (from five to ten, inclusive) and averages were determined for each group. Arranged in this way, the data indicated for PV an increase of 65 per cent above the average nonpregnant value, this peak being reached in the ninth lunar month rather than at term. During the tenth lunar month the increase amounted only to 52 per cent, and by the end of the second week post partum the normal nonpregnant level was reached. Similar curves were shown for TBV and RCV, with maximum increases in the

tration of dye at zero time is used in the usual formula^{7, 12, 15} to compute plasma volume, and from PV the TBV is found from the equation:

$$\text{Total blood volume} = \frac{\text{Plasma volume} \times 100}{100 - \text{hematocrit}}$$

When determinations are repeated in the same individual an initial so-called "dyed dye-free" sample of blood is obtained before injection of further dye, and the extrapolated value for concentration is corrected by subtracting the *L* value of the "dyed dye-free" sample. The method obviously is tedious and time-consuming, requiring from three and one-half to four hours to complete all of the steps in a single determination. We do not recommend it for routine clinical use.

Material

Twenty women at term (thirty-eight to forty weeks) with normal pregnancies were observed either before the onset of labor or early in the first stage. Repeat determinations were done on each of these women on the seventh postpartum day. Seven other women were given varying amounts of dye, while in labor or before cesarean section, and umbilical cord blood from these was examined for the presence of dye. Ten normal nonpregnant women from the gynecologic ward were used as control subjects.

Results

Controls.—In ten normal women of childbearing age TBV ranged from 3,070 to 4,500 c.c., and the mean was $3,974 \pm 140$ c.c. The range for PV was from 1,815 to 2,640 c.c., mean $2,326 \pm 78$ cubic centimeters. These values may

TABLE IV. THE PLASMA, TOTAL BLOOD, AND RED CELL VOLUMES FOR TWENTY NORMAL WOMEN IMMEDIATELY BEFORE AND SEVEN DAYS AFTER DELIVERY

CASE	AGE	PARA	WEIGHT AT TERM (POUNDS)	WEIGHT SEVENTH POST PARTUM DAY (POUNDS)	HEIGHT IN INCHES	AT TERM			SEVENTH POSTPARTUM DAY		
						PLASMA VOLUME IN C.C.	TOTAL BLOOD VOLUME IN C.C.	RED CELL VOLUME IN C.C.	PLASMA VOLUME IN C.C.	TOTAL BLOOD VOLUME IN C.C.	RED CELL VOLUME IN C.C.
1	23	iii	158	145	65	5855	8245	2390	3370	5000	1630
2	25	v	203	175	65	4970	7895	2925	3285	5650	2365
3	19	i	188	158	65½	4225	7260	3035	3160	4930	1770
4	29	0	176	157	66	3760	5960	2200	3320	5410	2090
5	30	iv	161	143	60½	3475	5860	2385	2570	4350	1780
6	19	0	136	115	62	3420	5440	2020	2890	5100	2210
7	23	iii	160	141	65	3385	5390	2005	2950	5000	2050
8	40	xv	153	132	65	3320	5090	1770	2850	4500	1650
9	28	vii	139	122	60	3295	5300	2005	2560	4370	1810
10	18	i	138	123	61	3205	5030	1825	2395	3720	1325
11	19	0	110	100	64½	3140	5050	1910	1755	3195	1440
12	22	i	171	155	61	2920	5025	2105	2255	3680	1425
13	19	0	130	114	62½	2875	4710	1835	2295	3910	1615
14	19	i	110	101	60	2850	4800	1950	2185	3840	1655
15	20	0	130	112	62	2775	4270	1495	1915	2910	995
16	22	i	144	132	60½	2670	4110	1440	2310	3870	1560
17	20	i	115	102	61½	2515	4170	1655	2195	3765	1570
18	20	0	119	100	61	2330	3695	1365	2280	3630	1350
19	18	0	127	115	62½	2300	3910	1610	2290	3875	1585
20	17	0	159	138	64	2250	3875	1625	1755	3025	1270

amounted to 18 per cent. In many cases the blood volume at the end of pregnancy was not outside the range of values found in nonpregnant women and the blood volume became more variable as pregnancy advanced. There was no significant difference between the mean blood volume at twelve weeks of gestation and the mean volume of the nonpregnant group, nor between the mean values at twenty-four and thirty-six weeks. However, the mean value at thirty-six weeks was significantly higher than that at twelve weeks (Table III).

TABLE III. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. FOR NONPREGNANT CONTROLS AND PREGNANT WOMEN AT VARIOUS STAGES OF GESTATION, CALCULATED FROM DATA OF ROSCOE AND DONALDSON

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R	P	SIGNIFICANT DIFFERENCE
Controls : 12 wks. ap.	50	158	0.32	0.7490	No
Controls : 24 wks. ap.	550	199	2.76	0.0058	Probably
Controls : 36 wks. ap.	1050	259	4.05	0.0001	Yes
12 wks. ap. : 24 wks.	600	175	3.42	0.0006	Yes
12 wks. ap. : 36 wks.	1100	205	5.35	0.0001	Yes
24 wks. ap. : 36 wks.	500	236	2.12	0.0340	No

Method

In recent years many techniques employing the blue azo dye, Evans blue (T-1824), for determination of plasma volume have been described, and the inexperienced worker may be at a loss to know which method to follow.¹⁰ We have combined the most desirable features from a considerable number of techniques, hoping to achieve the greatest possible accuracy. In general, we have combined the basic features of the original method of Gibson and Evans⁶ (adapted to the Evelyn¹¹ colorimeter by Gibson and Evelyn¹²) with the chromatographic extraction of Morris.¹³ The chromatographic technique of Morris has been perfected in our hospital by Hecht and Greenberg,¹⁴ and we are indebted to Dr. Hans Hecht for instruction in the use of this method which insures virtually complete recovery of Evans blue from plasma.

Briefly we proceed as follows: A previously standardized 0.35 per cent solution of Evans blue in distilled water is injected into an antecubital vein in 9 to 10 c.c. quantities, the exact amount being determined by weighing syringe, needle, and solution before and after injection according to the method of Price and Longmire.¹⁵ A torsion balance with a capacity of 120 Gm., accurate to ± 5 mg., is used for weighing the dye solution. At intervals of ten to fifteen minutes after the injection four to five samples of blood are removed through a 20-gauge needle from another antecubital vein, without stasis, or preferably from a femoral vein through an 18-gauge spinal-type needle which remains in situ until all samples have been drawn. The blood is collected in oxalated tubes and plasma removed after centrifugation at 3,000 r.p.m. for thirty minutes. Hematocrit values are obtained on the first and last samples. One cubic centimeter of plasma from each sample is mixed with 0.2 c.c. of 0.1 N sodium hydroxide solution, and 1 c.c. of this mixture is adsorbed on a column containing a mixture of aluminum oxide and magnesium oxide. The column is washed first with distilled water and then with an acetic acid-alcohol mixture to remove plasma proteins and pigments. Finally the Evans blue is eluted from the adsorbent with a mixture of hydrochloric acid and absolute alcohol, and the concentration of dye in the eluate is determined colorimetrically. Using the concentrations found at various times, a disappearance curve is plotted on semilogarithmic paper and is extrapolated to zero time (i.e., time of injection). The concen-

TABLE V. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN VALUES FOR PLASMA, TOTAL BLOOD, AND RED CELL VOLUMES IN CONTROL SUBJECTS, ANTEPARTUM PATIENTS, AND POSTPARTUM PATIENTS

GROUPS	PER CENT INCREASE OR DE- CREASE	DIFFER- ENCE BETWEEN MEANS	STANDARD ERROR OF DIFFER- ENCE	R	P	SIGNIFI- CANT DIFF- ERENCE
<i>Plasma volume—</i>						
Controls : term pts.	40.8	951	219	4.34	0.0001	Yes
Term pts. : pp. pts.	22.8	747	234	3.19	0.0014	Yes
Controls : pp. pts.		204	138	1.48	0.1389	No
<i>Total blood volume—</i>						
Controls : term pts.	32.2	1280	327	3.91	0.0011	Yes
Term pts. : pp. pts.	20.3	1067	344	3.10	0.0019	Yes
Controls : pp. pts.		213	227	0.94	0.3472	No
<i>Red cell volume—</i>						
Controls : term pts.	19.9	329	126	2.61	0.0091	Probably
Term pts. : pp. pts.	16.2	321	127	2.53	0.0114	Probably
Controls : pp. pts.		8	107	0.07	0.9442	No

average value for RCV was $1,657 \pm 76$ cubic centimeters. In each instance the postpartum values for PV and TBV were lower than the antepartum values, but in two patients (Cases 18 and 19) the decreases were scarcely worthy of mention. The average drop in PV amounted to about 23 per cent of the pre-delivery value, and for TBV the loss was 20 per cent. The differences between antepartum and postpartum mean values were statistically significant, with the possible exception of that for red cell volume (Table V). The difference of 204 c.e. between average PV in postpartum and nonpregnant women is *not* statistically significant, nor is the difference between postpartum TBV and the corresponding control value for nonpregnant subjects. Thus, it might be fair to say that in the main the postpartum average values have returned to the control levels by the end of one week.

Placental Transmission of Dye.—Seven women were given Evans blue in amounts ranging from 10 to 100 c.e. of a 0.35 per cent solution (i.e., from 35 to 350 mg. of dye) anywhere from twenty-five minutes to forty-eight hours before delivery of the placenta. In each case placental or fetal blood was obtained at delivery and examined by the chromatographic procedure described above. In only one instance was the colorimeter reading of sufficient magnitude to suggest the possible presence of an appreciable amount of dye, but in this sample (forty-eight hours after dye injection) no dye could be identified in a Beckman spectrophotometer. In the case of the patient who received 100 c.e. of dye solution, the maternal surface of the placenta was remarkably blue (three and one-half hours after injection), and the patient's lochial discharge had a bluish tinge for several days. Thomson and co-workers³ reported their inability to find dye in cord blood serum or amniotic fluid after giving 30 mg. of dye to three women in labor, nor could they detect any dye in placentas prepared by a special technique. They assumed, therefore, that dye did not disappear from the maternal blood stream by passing to the fetus. While our observations do not confirm this assumption beyond question, they at least suggest that, at most, only very minute amounts of dye are transferred across the placental barrier within the first few hours after injection. It is unlikely that the value for plasma volume is greatly magnified by loss of dye to the fetal circulation. On the other hand, our observation in the patient receiving the very large amount of dye (350 mg.) suggests the possibility that dye may be trapped in the placenta and thus removed from the maternal circulation. Selective localization of Evans blue in the placenta of rats has been reported by Brunsehwig and

be compared with those of Thomson and associates³ whose 28 normal women (From Gibson and Evans' larger series⁷) had a range of TBV from 3,030 to 4,870 c.e., mean $3,845 \pm 89$ cubic centimeters. Their mean value for PV was $2,324 \pm 54$ c.e., which is remarkably similar to our average value. RCV for our controls varied from 1,255 to 1,970 c.e., with a mean value of $1,649 \pm 75$ cubic centimeters. It seems fair to conclude that our method produces results which are similar in magnitude to the standards for normal women established by Gibson and Evans.

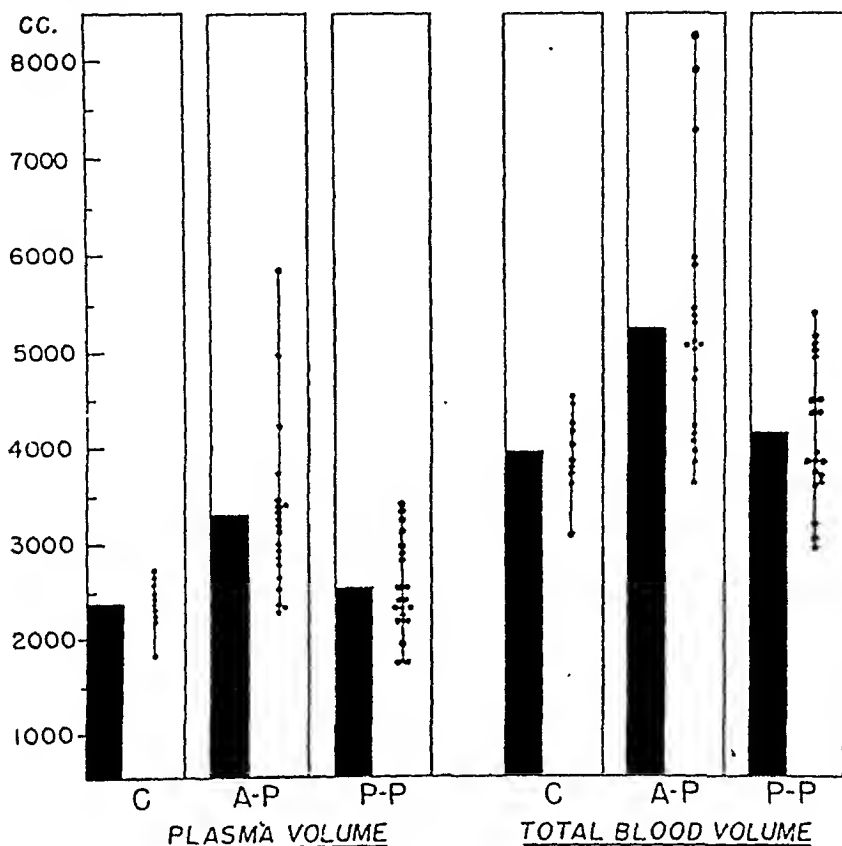


Fig. 2.—Plasma volume and total blood volume in control subjects (C), in normal women at term (A-P), and on the seventh postpartum day (P-P). The solid columns indicate the mean values, the perpendicular lines show the ranges, and the dots on these lines are individual values.

Pregnant Women at Term.—Twenty women (Table IV and Fig. 2) in this category had their blood volumes determined within two weeks of the delivery of a full-term infant. Twelve were studied on the day of delivery, the others at various times in the thirty-ninth and fortieth weeks of gestation. Plasma volumes varied from 2,250 to 5,855 c.e., the mean being $3,277 \pm 205$ c.e. The lowest value for TBV was 3,695 c.e., and the highest 8,245 c.e., with a mean of $5,254 \pm 296$ cubic centimeters. Red cell volumes ranged from 1,365 c.e. to 3,035 c.e. and the mean value was $1,978 \pm 102$ cubic centimeters. When compared with the nonpregnant series, PV and TBV were significantly greater in the pregnant women, while the significance of the increase in RCV was open to some question (Table V). At term the average increase in PV amounted to 41 per cent of the control value, and the increase in TBV to 32 per cent. The rise in RCV was only 20 per cent.

Postpartum Patients.—Seven days after delivery the same twenty women had plasma volumes (Table IV, Fig. 2) varying from 1,755 to 3,370 c.e., with a mean value of $2,530 \pm 114$ cubic centimeters. Correspondingly, TBV varied from 2,910 to 5,650 c.e., with a mean of $4,187 \pm 179$ cubic centimeters. The

applied to the study of blood volumes in pregnancy, but unfortunately the materials and apparatus required are rather elaborate and costly.

The authors of previous papers on blood volume in pregnancy have speculated freely on the cause or causes of the apparent increase in volume. Our study has not aided in the solution of this problem, nor has any significant new development along this line turned up in the past nine or ten years. The recent finding of Furth and Sobel²³ that granulosa cell tumors in mice were associated with hypervolemia revives the suggestion that increased estrogen levels are in some way concerned with elevation of the blood volume.

Summary and Conclusions

A chromatographic technique for extraction of Evans' blue from plasma has been used to determine plasma volume, and from this value the total blood volume is calculated by use of the hematocrit. Determinations were made on twenty normally pregnant women at term and on the same women seven days after delivery. A control group of ten normal nonpregnant women was used to check the results with our technique against previously determined standards for normal females.

At term the average value for plasma volume was about 40 per cent greater than PV in the control series and total blood volume was 32 per cent greater. While red cell volume appeared to rise about 20 per cent, the significance of this change was not so striking as in the case of PV and TBV.

Within a week after delivery, blood volume had returned virtually to non-pregnant levels.

Individual variation in blood volume during pregnancy is enormous. Standard deviations are relatively much greater for pregnant subjects than for either the controls or postpartum patients.

A few observations indicate that the dye-dilution method is not invalidated by transfer of dye across the placental barrier, but the question of dye being trapped at the placental site is still unsettled.

Data from several previous publications have been subjected to statistical analysis and certain unwarranted conclusions previously made have been critically reviewed.

It seems unlikely that anything yet published, including this report, has given a thoroughly reliable picture of what happens to blood volume in pregnancy. A great many more determinations should be made and the validity of dye techniques must be ascertained by the newer radioactive iron procedures for red cell volume.

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co-workers.¹⁶ We propose to study this phase of the problem more fully when suitable Negro subjects become available. In white women the massive doses of dye produce an undesirable bluish discoloration of the skin.

Comment

This study indicates that in all likelihood there is a significant increase in plasma volume and in total blood volume during the course of normal pregnancy. In our series the average increase at term in PV was about 41 per cent, and in TBV approximately 32 per cent. These values are higher than those suggested by Diekmann and Wegner,⁴ but for TBV the result is exceedingly close to the figure reported by Thomson and associates³ for women at term. Their increase for TBV, strangely enough, was identical with ours, but their increase in PV was about 10 per cent greater. However, Thomson's values at the ninth lunar month were considerably above those at term, particularly PV which seemed to have increased 65 per cent over the normal at that point. The statistical insecurity of these latter values has already been discussed in reviewing the literature.

Despite the apparent increase in volume where group averages are considered, it should be pointed out that the range of PV and TBV in pregnancy is enormous. Presumably there is a good deal of overlapping of the normal distribution curves for blood volume in pregnant and non-pregnant subjects, although there is no question about the significance of the difference between mean values for these groups (Table V). But when it comes to the individual patient, one is not justified in assuming that an increase in PV amounting to 40 or 45 per cent will have occurred by the fortieth week of gestation, or that a decrease of 23 per cent will be manifest within a week after delivery.

If the question of changing blood volume in pregnancy is to be further clarified and reliable standards established, a great many more determinations must be made at all stages of gestation, of parturition, and in the puerperium. We feel that the method employed in this study is not suitable for routine survey of a very large number of patients because it is far too time consuming. Recently we have employed the single ten-minute sample method advocated by Gregersen and others,^{10, 17, 18, 19} comparing this with the extrapolation of a disappearance curve. The values for PV obtained from a single sample are always a little greater than those found by using an extrapolated "L" value, but the increase amounts to only 3 or 4 per cent. If one is interested only in trends rather than absolute values the shorter procedure should be perfectly adequate, providing proper precautions are taken in obtaining and processing the single sample. We have assayed three different fractions of the ten-minute sample on separate chromatographic columns in order to detect errors in technique. As Gibson and others²⁰ have pointed out, there is no agreement that dye-plasma techniques measure with accuracy the TBV or circulating RCV, because the assumption that the hematocrit of blood flowing through the entire vascular bed is a constant at all times is probably erroneous. Using radioactive iron, they found RCV to be about 15 per cent less than when measured by the dye method. It is hoped that the newer radioactive iron techniques^{21, 22} may ultimately be

Finally, as still further evidence that the metabolic changes surrounding delivery are tied up with a loss of placenta, we have made studies on a case of abdominal pregnancy in which a living fetus weighing 4,000 Gm. was removed, the placenta being retained. Our index of change in metabolism was the change in the urinary excretion of sodium pregnandiol glucuronidate and nitrogen. For about three weeks following delivery there was a gradual decrease in the excretion of sodium pregnandiol glucuronidate, but with no change in the excretion of nitrogen. Then there was an abrupt fall in the excretion of sodium pregnandiol glucuronidate, indicative of cessation of production of progesterone. This deprivation of the body of progesterone (and probably estrogen) was followed by an increase in the excretion of nitrogen.

DR. GORDON DOUGLAS, New York City.—Dr. McLennan has reviewed the literature and applied critical statistical methods in an attempt to evaluate accurately the recorded data of this interesting subject. One is immediately impressed with the relatively small number of cases in any given series. This fact alone introduces difficulties in evaluating the data from a statistical point of view. The author deserves great credit for working on such a difficult problem. For each test it is necessary to have a willing "normal" patient who can hardly escape making the observation that she is the subject of investigation. Long, exacting, and tedious work in the laboratory must follow when a patient consents to subject herself to such investigation. It is very easy to say that a larger series of patients with repeated studies, conducted at various periods of gestation and the puerperium, would settle the problem. When individual variations in blood volume are so great, the importance of making repeated observations on the same patient becomes even more important. Perhaps newer techniques that Dr. McLennan has referred to will facilitate such investigation.

From a clinical point of view I think it particularly important that these studies be carried out to give us more exact information during the last four weeks of pregnancy and during the early puerperium. It is during this time that water retention followed by diuresis is such a frequently observed clinical phenomenon. Just what happens to the blood volume during this time has a very definite bearing on the management of pregnancy complicated by heart disease, toxemia, and other complications that are frequently encountered at this time.

The tremendous individual variations in blood volume recorded by the author confirms previously recorded figures. At the present time there is no entirely satisfactory explanation for the phenomenon. Dr. McLennan has pointed out the inaccuracies of the statistical data of Thompson and the fact that that claim cannot be substantiated. Additional studies may open a new horizon for the study of these poorly understood changes.

DR. MCLENNAN (Closing).—I am grateful to Dr. Allen for speculating on some of the reasons for these changes in blood volume. Obviously, time interfered with any mention of that on my part. That aspect of the subject, of course, could take up the entire space of a dissertation. And I am grateful to Dr. Douglas for pointing out the difficulties that arise in doing research of this kind. Patients begin to shy away from needles when they discover that a simple thing like blood volume requires six or eight venapunctures today and a repetition of that a week or so later. In order to overcome that hesitancy, we have resorted to the use of an indwelling femoral vein needle.

Dr. Douglas commented on the clinical manifestations, particularly the relation between the blood volume and the changes that occur in the cardiac patient. That is the one clinical field where blood volume studies have been most frequently employed; that is, the changes in blood volume have been pointed to as one reason perhaps for not terminating pregnancy three or four weeks before term, in view of the fact that many people have thought that blood volume decreases terminally, and therefore the cardiac condition improves, and there should not be any urgent reason for premature delivery. But this thesis has not been clearly proved.

I had no opportunity to mention that the Evans blue dye may escape in part to the placenta and get into the fetal circulation. A few people have tried to find out whether the dye can be recovered from the infant's blood. We tried to do this, and, while the data available are not thoroughly convincing, we suspect that very small amounts of this dye may be transferred across the placental site. Whether larger amounts of dye are actually trapped at the placental site is a question which no one has as yet properly answered.

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Discussion

DR. WILLARD ALLEN, St. Louis, Mo.—Dr. McLennan's paper brings a surprising and pleasing note to the meetings. Here is a paper by an obstetrician and gynecologist who utilizes one of the newest tools of the chemical laboratory as an aid for the study of an old problem. I refer to chromatographic absorption. He then subjects his final figures to rigid statistical analysis. The figures he has obtained leave no room for any doubt concerning the presence of a marked decrease in blood volume in the first week after delivery. Each one of twenty patients studied showed a lower blood plasma volume on the seventh postpartum day than they did at term. This obviously is significant. I do not have a sufficiently good grasp of the levels of significance of the standard errors to elaborate on this point. I need only mention, however, that where the observations are consistent for 20 successive observations, the probability of the result being due to chance is extremely remote.

I have taken the liberty of doing some additional calculations from his data, just to enable me to make some remarks on the role which the sex hormones probably play in the metabolic changes occurring in pregnancy. Dr. McLennan is fully aware of the significance of his observations, but I think in his desire to confine himself only to the facts, he has omitted any remarks about the possible origins of these changes in blood volume which he has observed. Being only a discussor, I can be forgiven perhaps for indulging in some speculation.

The average loss of weight in his twenty patients was 17 pounds. If we allocate 10 pounds of this to the baby, placenta, and amniotic fluid, there still remains 7 pounds. This is only 5 per cent of the weight of the mother (minus the 10 pounds assigned to the baby, placenta, etc.). Now recall that the decrease in blood volume is approximately 20 per cent. This shows that the decrease in blood volume is not explained simply by the decrease in weight of the patient. This simple calculation only serves to emphasize the magnitude of the decrease and to provide grounds for speculation on the cause.

It seems to me quite clear that the metabolic change occurring during pregnancy can be attributed to the presence in the maternal organism of large amounts of estrogens and progesterone. Also, there is ample evidence that these sex hormones come from some source other than the ovaries in the woman. The evidence all points to the placenta as the extra-gonadal source. The delivery of the placenta suddenly deprives the woman of her sex hormones. She is, in fact, relatively more deficient in hormones four or five days post partum than at any other time in her life. It is because of the deficiency that she lactates. It seems easy to assume that the metabolic changes such as the loss in weight, the increased excretion of nitrogen, the decrease in blood volume—to mention only three—are brought about by the deficiency of sex hormones induced by the delivery of the baby and placenta. The argument would, of course, be less fanciful if there were some shreds of evidence on the positive side. Fortunately there are. In the monkey the fetus has been removed leaving the placenta intact. Such animals, deprived of their babies but retaining functioning placentas, continue to gain in weight. The placenta is delivered at term, whereupon the monkey returns to her pre-pregnant weight.

cent noted by Lynch. Such figures may be unreliable since the accuracy of the patient's knowledge of her family medical history is often open to question. Eight patients or 9.8 per cent of eighty-one in whom chest examinations were recorded had pleural effusions. Two of these had minimal pulmonary tuberculosis. Ureteral obstruction was noted in five patients although only a few had studies of the upper urinary tract. The blood sedimentation was rapid in thirty-eight and normal in fourteen of these cases where it was recorded.

Twenty-three patients had previous operations. Three had intrauterine radium for benign bleeding thirteen, ten, and seven years previously. Three had vaginal plastic operations (one with hernia repair) nine, seven, and three years previously, and one had a small dose of radium to the cervix four years before for a lesion that proved to be benign. Four had abdominal pelvic operations from fifteen to twenty years before. Three patients had abdominal operations one year previously. One of these had an umbilical hernia repaired, one had an operation for an ovarian abscess, and one had a supravaginal hysteromyomectomy. The latter patient, who was 37 years of age was operated upon on our service, the ovaries appeared to be normal and were conserved. She had an inoperable bilateral solid carcinoma when readmitted one year later. Seven patients had mastectomies performed from four to twenty-three years previously, but we do not know how many actually had cancer of the breast. One had a cholecystectomy four years before and one had a resection of her stomach sixteen years before coming under our care. Two patients had refused operation for pelvic tumors, two and ten years previously.

The chief symptoms mentioned were pain in fifty-three instances and enlargement of the abdomen in fifty-nine, a large proportion of patients exhibiting both. Nausea and vomiting, loss of weight, backache, weakness, and dyspnea were mentioned less often. Eleven, or 14 per cent of the patients complained of bleeding; six of these had associated uterine fibroids. The duration of symptoms from time of onset until admission to the hospital may be listed as follows:

Less than 1 month	8
1 to 3 months	13
3 to 6 months	13
6 to 12 months	21
12 or more months	19
Not stated	10

Thirty-seven patients complained of vague gastrointestinal symptoms other than constipation for six months or longer.

It has been our policy to operate upon all patients whose physical condition would permit of surgery, even though the growth appeared to be extensive. The primary tumor was removed whenever possible. The omentum was excised only if involved by a growth that was otherwise limited to the pelvis. The tendency to attempt surgery in many advanced cases, in part explains our mortality rate of 17 per cent, since nine of the fourteen postoperative deaths occurred in patients with very far advanced malignancy. The following operative procedures were done:

Supravaginal hysterectomy and bilateral salpingo-oöphorectomy	18
Supravaginal hysterectomy and unilateral salpingo-oöphorectomy	3
Total hysterectomy and bilateral salpingo-oöphorectomy	4
Bilateral salpingo-oöphorectomy	10
Unilateral salpingo-oöphorectomy	14
Exploratory only	33
Died without operation—autopsied	2

Three patients who originally had postoperative x-ray therapy were reoperated upon later. In one a recurrence was removed nine years after the original operation. The others, in both of whom only an exploratory operation

MALIGNANT TUMORS OF THE OVARY*

JOHN B. MONTGOMERY, M.D., PHILADELPHIA, PA.

(From The Division of Gynecology, Department of Obstetrics and Gynecology, The Jefferson Medical College Hospital)

THIS study consists of a brief review of all of the cases of malignant disease of the ovary that were treated in the Division of Gynecology of the Department of Obstetrics and Gynecology in the Jefferson Medical College Hospital between Oct. 1, 1921, and Oct. 1, 1946. The clinical and pathologic records have been reviewed, and all histologic slides have been re-examined in collaboration with Dr. Peter A. Herbut. The original pathologic diagnoses were made by Baxter L. Crawford, M.D., (deceased), C. J. Buchner, M.D., and Jacob Hoffman, M.D.

Material

One hundred nineteen cases were available for study. Twelve of these, all with advanced carcinoma, have been discarded because the microscopic slides were not available or the diagnosis was in doubt. Of the remaining 107 cases, eighty-four were primary carcinomas of the ovary, seven were large carcinomatous tumors of the ovary secondary to uterine cancer, two were adenocarcinomas occurring in teratomata, ten were granulosa cell tumors, one was a Krukenberg tumor, two were dysgerminomas, and one was a Brenner tumor. Although our interest centers in the adenocarcinomas, the record of our end results in ovarian malignancy would be incomplete if we were to exclude the other types mentioned from our study. They will be reviewed separately.

The ages of the eighty-four patients with adenocarcinoma may be recorded in decades as follows:

Years	Patients
Under 20	1
20 to 29	8
30 to 39	14
40 to 49	27
50 to 59	21
60 to 69	12
70 to 79	1

Forty-eight, or 57 per cent, were between the ages of 40 and 60 years. The youngest was 16 and the oldest 73 years. Seventy patients were white, eleven were Negroes, and in three the race was not stated. Seventy were married, fourteen, or 16.6 per cent, were single. (This corresponds to Lynch's 17 per cent and Pemberton's 19 per cent.) Only eight, or 11.4 per cent, of the married women were sterile. This is much lower than the 31 per cent reported by Lynch and the 22 per cent in Pemberton's series. Of the sixty-two women who had conceived, eight, or 13 per cent, did not carry their pregnancies to term. In four cases the parity was not stated. Thirty-one patients had passed the menopause, in three of these the amenorrhea had been induced by radiation. There was a family history of cancer in ten instances or 13.6 per cent of seventy-five cases in which this was recorded in the history. This is far below the 40 per

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947

TABLE I. SUMMARY OF RESULTS—GRADE I MALIGNANCY

<i>Serous Papillary Adenocarcinoma</i>											
	PA-TIENTS	UNILAT- ERAL	BILAT- ERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN FIVE YEARS		DEAD		UNTRACED INCOMPLETE X-RAY	
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY		
Completely operable	6	3	3	2	1	0	1	1 yr. Cause?	0	1	
Incompletely operable	5	1	4	3	0	0	0	6½ yr. P.O.D.	1	0	
Exploratory	3	0	3	1 12 yr. ♂ disease	0	1 1½ yr. ♂ disease	0	1 6 yr.	0	0	
Total	14	4	10	6	1	1	1	3	1	1	
<i>Pseudomucinous adenocarcinoma</i>											
Completely operable	5	5	0	2	2	0	0	0	1 8 years Cause?	0	
Incompletely operable	2	1	1	0	0	1 3 yr. inad- equately	0	1 6½ yr.	0	0	
Exploratory	0	0	0	0	0	0	0	0	0	0	
Total	7	6	1	2	2	1	0	1	1	0	
Grand Total	21	10	11	8	3	2	1	4	2	1	

was done originally were still inoperable after one and eleven years, respectively. Unilateral oöphorectomy was done in seventeen patients, one of whom had one ovary removed twenty years previously. In three of these the growth was extensive and in five the patient's condition did not warrant further surgery. Of the eight in which an apparently normal ovary was deliberately conserved, one is untraced, one died of an undetermined cause at the end of eight years, having had a normal pregnancy four years before, and six are living and free of disease for more than five years.

We have studied our cases in the light of the four outstanding factors that generally are regarded as governing the end results in ovarian carcinoma, (a) the extent of the growth or the operability, (b) the grade of malignancy, (c) the histologic type of tumor, and (d) the influence of x-ray therapy on the lesion. Throughout the study, where possible, we attempt to show the interrelationship of these factors.

The group of eighty-four primary adenocarcinomas have been classified as either serous or pseudomucinous. Where the growth was anaplastic (Grade III), occasionally there was some doubt as to the correct histologic diagnosis but as a rule such cases appeared to be serous and were classified as serous carcinomas. Although the gross structure of the tumors has been regarded as of secondary importance we have further divided them into cystic, partly solid and partly cystic, and solid growths. This has been done in recognition of the fact that the tumors of solid consistency are more actively malignant than those whose structure is largely cystic or papillary.

Grade of Malignancy

Most reports indicate that the best results can be expected in those patients with well differentiated tumors. On the other hand "grading" is generally thought to be of little value in prognosis of ovarian carcinoma. However, as Taylor suggests "if the recognition and segregation of the well differentiated group may be termed 'grading' then the grade of malignancy in ovarian carcinoma is of enormous prognostic significance." It is from such a viewpoint that we have divided our cases into three histologic grades of malignancy as suggested by Taylor and as employed by us in a previous contribution to this subject.

Grade I or Low Grade Malignancy.—Tumors in which well differentiated columnar epithelium lined the glands and cystic spaces, the adult structure being maintained throughout except in occasional areas where there was slight infiltration, a piling up of epithelial cells into two or more layers and slight nuclear changes.

Grade II or Intermediate Grade Malignancy.—Tumors that are actively malignant but which show definite glandular or papillary structures.

Grade III or High Grade Malignancy (Anaplastic).—Undifferentiated epithelial cells with marked nuclear changes growing in strands or solid areas with little or no glandular or papillary structure.

Grade I Carcinoma.—(Table I.) Twenty-one cases; fourteen serous and seven pseudomucinous adenocarcinomas. Eleven patients are living from five to twenty-four years. Ten of these are free of disease and one, in which an exploratory operation was done twelve years ago and who was reoperated upon one year ago, still has evidence of extensive pelvic malignancy. Seven of the

five-year survivors had tumors of the serous type of which three were completely operable and three incompletely operable, while in one only an exploration was possible. All but one received deep x-ray therapy. In the three completely operable cases the growth was unilateral. The four remaining five-year survivors had unilateral, completely operable pseudomucinous tumors two of whom received deep x-ray therapy.

Three patients with Grade I tumors are living for less than five years after operation. Two had tumors of the serous type, one was removed completely but only exploration was possible in the other. The third patient had an incompletely operable pseudomucinous tumor. The completely operable patient received no x-ray therapy while the other two received only a small amount.

Six patients with Grade I malignancy are dead, and one is untraced. Four of these had tumors of the serous type of which one was completely operable, two incompletely operable and one had only an exploration. One patient with an incompletely operable tumor died as a result of the operation. The other three received deep x-ray therapy. The patient whose tumor was removed completely died one year later of an undetermined cause, but the other two died of malignancy after six and one-half years. Two patients who died had pseudomucinous tumors. One whose tumor was completely removed, subsequently had a normal pregnancy, but died eight years after operation of an undetermined cause. The other with an incompletely operable tumor received x-ray therapy but died of malignancy after six and one-half years.

Grade II. Carcinoma.—(Table II.) Twenty-three cases; nineteen serous and four pseudomucinous adenocarcinomas. Four are living. Three are free of disease from five to twenty years after operation, and one has a recurrence in the cervix after seven years. Three of the four survivors had bilateral tumors of the serous type. In one of these the growth was removed entirely but in two instances the operation was incomplete. The fourth survivor had a completely operable, unilateral pseudomucinous adenocarcinoma. All four received deep x-ray therapy. Eighteen patients with tumors of Grade II malignancy are dead (four as a result of the operation), and one is untraced. Eleven of these received deep x-ray therapy, but the dosage was adequate only in seven. Of these receiving a full course of x-ray, one patient with a completely operable unilateral cystic and solid tumor of the serous variety survived for four years and one with an incompletely operable bilateral solid growth of the same type lived for three years, one patient with an inoperable serous tumor died in thirteen months, and two others with partly cystic and partly solid tumors died of malignancy after one and one-half years and six months, respectively. One patient with an inoperable pseudomucinous tumor survived for three years, and one with incompletely operable pseudomucinous growth died of malignancy after one and one-half years. The four with inadequate radiation all had advanced serous tumors and died of malignancy in less than six months. Of the seven patients who did not receive x-ray therapy four died as a result of the operation, one with incompletely operable tumors and two in whom only exploration could be done survived for eight months, two months, and eleven months, respectively.

Grade III Carcinoma.—(Table III.) Forty cases; thirty-nine serous and one pseudomucinous carcinoma. One patient is living and free from evidence of malignancy twenty-one years after complete removal of a unilateral serous papillary adenocarcinoma (partly solid and partly cystic) followed by deep x-ray therapy. Two are living and free of disease for less than five years. In one of these the tumor was unilateral with local extension, not all of which could be removed and the other had bilateral tumors with a nodule in the omentum, completely operable. The first patient received x-ray therapy, the second did not. Thirty-five are dead, ten postoperatively. Of the twenty-five

TABLE II. SUMMARY OF RESULTS GRADE II MALIGNANCY

<i>Scrous Papillary Adenocarcinoma</i>										
	PA- TIENTS	UNI- LATERAL	BI- LATERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN 5 YEARS		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	
Completely operable	4	3	1	1	0	0	0	1	2	0
Incompletely operable	10	4	6	2 1 re- cur 7 yr.	0	0	0	4 yr.	P.O.D. 4	0
Exploratory	5	0	5	0	0	0	0	1-3 yr.	3 P.O.D.	0
Total	19	7	12	3	0	0	0	2 inadequate	8	0
<i>Pseudomucinous Adenocarcinoma</i>										
Completely operable	1	1	0	1	0	0	0	0	0	0
Incompletely operable	2	0	2	0	0	0	0	2	0	0
Exploratory	1	0	1	0	0	0	0	1 inadequate	0	0
Total	4	1	3	1	0	0	0	3 yr.	0	0
Grand Total	23	8	15	4	0	0	0	11	0	0

TABLE IV. RESULTS IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

	PATIENTS	LIVING AND FREE OF DISEASE FIVE YEARS PLUS	
		NUMBER	PER CENT.
Serous Papillary Adenocarcinoma Grade I	10	6	60
Pseudomucinous Adenocarcinoma Grade II	6	4	66.6
Serous Papillary Adenocarcinoma Grades II and III	48	3	6.2
Pseudomucinous Adenocarcinoma Grades II and III	4	1	25
Total	68	14	20.5

TABLE V. RESULTS IN RELATION TO GRADE OF MALIGNANCY IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

MALIGNANCY	TOTAL CASES		FREE OF DISEASE FIVE YEARS	
	NUMBER	PER CENT	NUMBER	PER CENT
Grade I	16	23.5	10	62.5
Grade II	19	27.9	3	15.8
Grade III	33	48.5	1	3.0
Grades II and III	52	73.5	4	7.7

that we may expect somewhat different results in these two groups. This difference, however, may be due to the fact that there is a definite relationship between the grade of malignancy and the extent of the growth in many of our cases in these two groups. As a rule the growth was much further advanced in Grade III cases; in twenty-six, or 65 per cent, of forty patients in this group, only exploration could be done—while only six, or 26 per cent, of the Grade II cases were inoperable. In the incompletely operable patients the growth as a rule was less extensive in Grade II than in those with Grade III carcinoma. The three living patients who had Grade III cancer all had unilateral completely operable papillary cysts.

The high percentage of survivors in the group with Grade I malignancy may be due to the well-known difficulties in histologic diagnosis in this group. Errors are inevitable, and the desire to err on the side of safety perhaps accounts for the inclusion of some cases of doubtful malignancy in this group. Taylor and others have reported cases in which careful follow-up observations have made it obligatory that the original diagnosis be changed. Two of our cases illustrate this difficulty.

M. Y., aged 32 years, had bilateral salpingo-oophorectomy performed at the Jefferson Hospital on Dec. 11, 1923, for bilateral papillary ovarian cysts which involved the right broad ligament. The histologic diagnosis was papillary cystadenoma of the ovaries (nonmalignant). Because of the grossly invasive nature of the growth, the patient was given deep x-ray therapy prophylactically. She remained well and free from evidence of disease until May, 1932. Reoperation revealed a cauliflowerlike growth about the size of an orange originating between the layers of the right broad ligament and extending on to the adjacent peritoneum. The mass was excised and she was again given x-ray therapy (4,500 r in air over four portals). The histologic diagnosis was papillary adenocarcinoma. When last examined on Jan. 2, 1940, she was well and free from palpable evidence of malignancy. In a recent communication from another city she reported that she is in excellent health.

M. H., aged 23 years. Bilateral salpingo-oophorectomy and supravaginal hysterectomy was done on Jan. 3, 1935, for large bilateral ovarian tumors which

who survived the operation seventeen received x-ray therapy and eight did not. In eight of these treated by x-ray the tumors had been removed in part and in the others nothing more than an exploratory section was done. Of the former group one died in eight months, two died in one and one-half years, one in one and three-fourths years, one in two and one-half years, and three survived for three years, although one had inadequate therapy. Among the nine patients who had only exploratory operations, one is untraced and two with inadequate x-ray survived less than two months. The others died in seven months, 7 months, ten months, one and one-half, one and one-half, and one and two-thirds years, respectively. In eight of the nine patients who survived the operation but died without x-ray therapy the growth was altogether inoperable, while in one only an incomplete operation was done. One of these survived for ten months, but the others all died of malignancy in less than four months.

TABLE III. SUMMARY OF RESULTS GRADE III MALIGNANCY

SEROUS PAPILLARY ADENOCAR- CINOMA	PA- TIENTS	UNILAT- ERAL	BILAT- ERAL	LIVING 5 TO 21 YEARS		LIVING LESS THAN 5 YR.		DEAD		UN- TRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY
Completely op- erable	3	3	0	1	0	0	1	0	1	0
Incompletely operable	11	5	6	0	0	1 4 yr.	0	8	2 1 P.O.D.	0
Exploratory	25	0	25	0	0	0	0	8 3-3 yr.	15 8 P.O.D.	2
Total	39	8	31	1	0	1	1	16	18	2
Pseudomucin- ous explora- tory	1	1	0	0	0	0	0	0	1 P.O.D.	0
Grand Total	40	9	31	1	0	1	1	16	19	2

Twenty-one of the entire group of eighty-four patients with primary adenocarcinoma of the ovary are living. Fourteen of these had tumors of Grade I malignancy, four had Grade II, and three had Grade III malignancy.

Sixty-eight of the eighty-four patients were treated before Oct. 1, 1941, and therefore are eligible for five-year study. In Table IV the five-year results in each of the three grades of malignancy are presented in relation to the histologic type of the tumors. It will be noted that the five-year salvage of 20.5 per cent is due largely to the fact that ten of the fourteen patients who are free of disease had tumors of Grade I malignancy. The five-year results in relation to grade of malignancy alone are presented in Table V. The high percentage of survivors in the Grade I group is very striking. The effect of this Grade I on the five-year results is seen even more clearly when the cases in Grade II and Grade III are combined. The total is fifty-two, or 73.5 of the sixty-eight cases that are eligible for five-year study, and only four, or 7.7 per cent are free of malignancy for five or more years.

These figures emphasize the striking influence of "grading" in the prognosis of ovarian cancer and are in line with the findings of Taylor who reported twelve cures among thirty-six Grade I cases, but only two among fifty-two undifferentiated types. Although the influence of the well-differentiated tumors is well recognized generally, failure to take these into consideration undoubtedly accounts for the high percentage of cures that sometimes are reported. Although many believe that segregation of the actively malignant tumors into Grade II and Grade III malignancy probably has little prognostic value, our experience based on results shown in Tables I to III and in Table V suggest

Table VII presents the results in relation to the extent of the growth in the sixty-eight cases that are available for five-year study.

TABLE VII. RESULTS IN RELATION TO EXTENT OF GROWTH IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

	PATIENTS	PER CENT	FREE OF DISEASE FOR FIVE YEARS	
			PATIENTS	PER CENT
Completely operable	18	26.5	10	55.5
Incompletely operable	20	29.4	4	20.0
Exploratory	30	44.1	0	0.0
Total	68	100	14	20.5

Type of Tumor

Adenocarcinoma.—There were eighty-four cases of adenocarcinoma; of these, seventy-two, or 85.7 per cent, were serous, and twelve or 14.3 per cent, were pseudomucinous adenocarcinomas. The relation of the grade of malignancy, the extent of the growth, and the influence of x-ray therapy, to the end results in these two groups as shown in Tables I to VII have been discussed previously. Although the total number of pseudomucinous tumors is small, our results substantiate the frequently stated view that these tumors are less malignant than the serous variety among which there is a much larger proportion of incompletely operable and inoperable tumors.

Of the sixty-eight patients who were treated more than five years ago, fifty-eight had serous papillary adenocarcinomas of whom nine or 15.5 per cent, are living and free of disease for more than five years, while of the ten with pseudomucinous tumors, five, or 50 per cent, have survived for five or more years without recurrence.

It is well known that at least three pathologic entities based on the gross characteristics of the tumor which are encountered frequently are of considerable prognostic importance. These are the papillary cysts, the partly solid and partly cystic tumors, and the solid tumors. From Table VIII it will be seen that twelve of the sixteen patients who are living for five or more years had papillary cysts (ten of these were of Grade I malignancy). Only four of the thirty-seven with partly solid and partly cystic tumors have survived more than five years, and all of the eighteen who had solid carcinomas are dead.

TABLE VIII. RESULTS IN RELATION TO GROSS TYPE OF TUMOR

	PATIENTS	UNILATERAL	BILATERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN FIVE YEARS		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	
Papillary cyst-adenocarcinoma	20	12	8	9 2 with disease	3	0	0	5	3 3 P.O.D.	
Solid and cystic adenocarcinoma	37	10	27	4	0	3	2	14 4 inadequate	13 18 yr. 8 P.O.D.	1
Solid adenocarcinoma	18	3	15	0	0	0	0	8 2 inadequate	9 4 P.O.D.	1
Undetermined	9	1	8	0	0	0	0	5 3 inadequate	3	1

were adherent. The histologic diagnosis was pseudomucinous cystadenoma of both ovaries, malignancy doubtful. X-ray therapy was withheld until six months later when a small mass was noted in the cul-de-sac. The diagnosis was changed to pseudomucinous cyst adenocarcinoma.

Extent of the Growth

The gross extent of the disease, of course, is recognized as the most important factor in prognosis. We have divided our cases into three groups according to their operability, namely, those in which all of the tumor was removed (completely operable); those in which the tumor was removed only in part (incompletely operable); and those in which only an exploratory operation could be done. Such a grouping has the advantage of simplicity, but fails to take into account such influences as rupture of the tumor during operation, or adhesions in the completely operable group, and the extent of the disease in those that are incompletely operable.

Table VI presents the results in the eighty-four cases of adenocarcinoma from the viewpoint of the gross extent of the disease and in relation to the type of tumor and the influence of x-ray therapy. The tumor was completely operable in nineteen, or 22.6 per cent. Ten of these are free of evidence of disease from five to twenty-four years, and two for less than five years. Thirty, or 35.7 per cent, were incompletely operable, of which only four were free of gross disease for more than five years. Thirty-five, or 41.6 per cent were inoperable, but one of these is alive with extensive disease still present twelve years, and one is alive one and one-half years after surgical exploration. The relation of grade of malignancy to the extent of the growth has been discussed in the preceding section and indicated in the accompanying tables.

TABLE VI. SUMMARY OF RESULTS IN RELATION TO EXTENT OF GROWTH AND TYPE OF TUMOR

	PA- TIENTS	UNILAT- ERAL	BILAT- ERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN 5 YEARS		DEAD		UN- TRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	
<i>Scrous Papillary Adenocarcinoma</i>										
Completely op- erable	13	9	4	4	1	0	2	2	2	2
Incompletely operable	26	10	16	5 1 with disease	0	1	0	13	7	0
Exploratory	33	0	33	1 with disease	0	1 with disease	0	12	17	2
Total	72	19	53	10	1	2	2	27	26	4
<i>Pseudomucinous Adenocarcinoma</i>										
Completely op- erable	6	6	0	3	2	0	0	0	1	0
Incompletely operable	4	1	3	0	0	1	0	3	0	0
Exploratory	2	1	1	0	0	0	0	1	1	0
Total	12	8	4	3	2	1	0	4	2	0
Grand Total	84	27	57	13	3	3	2	31	28	4

Treatment was given usually over four ports, though occasionally in thin persons only three were used.

After January, 1925, the following factors were used: 20 to 30 milliamperes, 175 to 200 kilovolts, filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin target distance, through ports 16, 19, 20 cm. square. The erythema value from January, 1925, to August, 1930, was 970 r, and since August, 1930, has been 800 r. There has been no major change since 1930, although in recent years the four fields have been reduced to 10 by 15 cm. except in patients with broad pelves when they are widened to 15 by 15 cm. Previous to 1942 patients were treated on alternate days, so that at the end of four weeks the effective depth dose was from 1,600 to 2,000 r. Since that time they have been treated daily with 125 to 250 r, depending on tolerance. When disease is known to be widespread, four additional fields cephalad to the pelvic ports are used, or two fields may be substituted covering the area from xiphoid to pelvis. With very large fields and with small fields in obese women, the T.S.D. is increased to 80 cm. The total dosage given is 2,000 to 3,000 r per field, except with large fields when it is reduced to 1,000 to 1,500 r. Any patient who receives less than 1,200 r to each of four 10 by 15 cm. fields is regarded as inadequately treated. In recent years there has been insistence on small daily dosage with attention to avoid diarrhea and vomiting with less tendency to multiple series of treatments.

We have urged x-ray therapy in all patients whose general physical condition warrants it, except those with extensive upper abdominal metastasis. It is of utmost importance that the roentgenologist be acquainted with the location and gross extent of the malignancy so that he may outline the fields and direct the rays to the best advantage. There is some risk of damage when the treatment is pushed to the limit. One of our patients developed agranulocytosis and another an ulcerative colitis.

When the results from x-ray therapy are studied in relation to the grade of malignancy, it will be seen as noted previously that in Grade I (Table I), eight of eleven five-year survivors received deep x-ray therapy. In three of these the tumor was not completely removed, while in one only an exploratory operation was done. Four of these patients are living for more than ten years, one with evidence of disease still present. All three who survived five years without x-ray therapy had completely operable tumors. Among those who have died following x-ray therapy three survived for six and one-half years. However, since patients with tumors of this Grade of malignancy are known to survive for more than five and occasionally for more than ten years without x-ray, its value in this group is uncertain. In Grade II (Table II) malignancy the influence of x-ray therapy was more definite, since two of the five-year survivors who were so treated had incompletely operable tumors—although one now has a recurrence. The duration of life was probably prolonged in seven other patients in this group. In Grade III (Table III), one patient with an incompletely operable tumor who received x-ray is free from evidence of malignancy for four years after operation. Among seven who survived the operation but died subsequently, the duration of life was apparently prolonged.

Granulosa Cell Tumors.—There were ten cases, or 9.3 per cent, of the entire group of 107 cases of malignant tumors of the ovary. Three are dead. One died of cerebrospinal syphilis three years after operation, one died eight weeks after operation as a result of x-ray damage to the large bowel, and one whose tumor regressed on three occasions following x-ray therapy died of malignancy eight years after incomplete operation. The latter two were regarded originally as anaplastic carcinomas. They were included in a previous report emphasizing the value of x-ray therapy in ovarian cancer. Four are living and free of disease, three for more than five years. One of these who has survived eleven years was given x-ray therapy under the mistaken diagnosis of anaplastic carcinoma. Three patients in this group are untraced.

Ovarian Carcinoma Associated With Adenocarcinoma of Endometrium.—There were seven cases, or 6.5 per cent, of the entire group. The growth apparently originated in the uterus in all, although in two instances this was somewhat doubtful. In one of these there was an anaplastic squamous cell carcinoma of the cervix with a solid papillary adenocarcinoma of the ovary in which some areas showed a lesion identical with that in the cervix. The other patient had carcinoma involving the entire endometrium and a unilateral papillary adenocarcinoma of the ovary, some areas of which contained epithelial elements resembling pseudomucinous carcinoma. This was regarded as probably of endocervical origin. Two patients had been treated with intrauterine radium for endometrial carcinoma two and four years before operation for the ovarian tumor, and one had received x-ray therapy without curettage on two occasions during the previous ten years for supposed benign bleeding. Six patients are dead, one as a result of operation. Two died within six months, the other three each of whom received deep x-ray therapy lived one and one-half, three and three-fourths and seven years, respectively. One patient is living and free of evidence of disease one and one-half years after total hysterectomy and bilateral salpingo-oophorectomy followed by deep x-ray therapy.

Special Group.—There were two dysgerminomas—one patient was a girl 16 years of age, and the other was twenty-eight years of age. They have remained well for twenty-four years and three years, respectively. The 16-year-old patient was reported in 1925 by Dr. Lewis C. Scheffey as a sarcoma of the ovary. Two adenocarcinomas developed in teratomas. Both patients are dead, one died of cardiac failure three weeks after complete removal of bilateral tumors, the other survived for one year after removal of a large adherent solid tumor followed by x-ray therapy. One patient who had a Brenner tumor was well when last examined eight years after operation. She is untraced for seven years. One patient with a Krukenberg tumor died within three months after operation.

X-ray Therapy

The factors used in administering x-ray therapy have varied somewhat since our first case was treated in 1924. Two methods have been used. Prior to August, 1927, massive doses were given at a single sitting at right angles to one of three or four pelvic ports. The amount given was that which the skin would tolerate, and the entire course was completed in three or four days. The factors were 3 milliamperes, 170 to 200 kilovolts filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin target distance through ports 16, 19, or 20 cm. square. An erythema was obtained with 270 milliampere minutes of treatment. After August, 1927, the saturation method was used.

TABLE IX. RESULTS IN 107 MALIGNANT TUMORS OF THE OVARY

MALIGNANT TUMORS OF THE OVARY	TOTAL PATIENTS		PATIENTS ELIGIBLE FOR FIVE- YEAR STUDY		
	NUMBER	LIVING—NO MALIGNANCY	NUMBER	FREE OF DISEASE FIVE YEARS PLUS	
				NUMBER	PER CENT
Primary adenocarcinoma	84	18	68	14	20.5
Adenocarcinoma secondary to uterine cancer	7	1	4	0	0
Adenocarcinoma in a teratoma	2	0	2	0	0
Granulosa cell tumors	10	4	9	4	44.4
Dysgerminoma	2	2	1	1	100
Krukenberg tumor	1	0	1	0	0
Brenner tumor	1	Untraced after 8 yr.	1	0	0
Total	107	25	86	19	22.0

All untraced patients are counted as dead.

Comment

Operability and grade of malignancy are undoubtedly the factors that govern the percentage of survivals for five or more years. So far as type goes the papillary cysts are the most favorable and if they are completely operable one may safely predict that at least 50 per cent will be alive and free of disease for more than five years. On the other hand, it is agreed by all that the number of five-year survivors among those who have actively malignant tumors of the partly cystic and partly solid, or of the solid type is pitifully small. This result is influenced by the fact that the vast majority of such tumors do not come under observation until the growth is far advanced. The difficulties in achieving an early diagnosis in carcinoma of the ovary seem almost insurmountable. Many are "silent" or nearly so. Yet we have found in reviewing the histories that 37 per cent of our patients had abdominal symptoms, mostly referable to the gastrointestinal tract for six months to several years before a pelvic examination was made. One patient, the sister of a physician, was given "samples" for "indigestion" for three years before her abdomen began to swell. Another had been treated for "colitis" for four years and had a complete medical survey in a hospital less than one year before large bilateral ovarian tumors were discovered on routine pelvic examination. It is not uncommon for abdominal enlargement to be the first sign of trouble.

Such instances suggest that repeated routine pelvic examinations in all women may be needed to solve the problem of early diagnosis but even then some may be overlooked. The studies of Dr. Catharine Macfarlane are very interesting in this respect. Among 1,370 apparently healthy women who presented themselves for routine pelvic examination and of whom 670 have reported for re-examination every six months for nine and one-half years, one ovarian carcinoma was encountered. This tumor which was reported to be the size of an orange was not present when the patient was examined six months previously. That a malignant tumor of the ovary may develop with great rapidity is indicated by the far advanced carcinoma that was found in one of our patients

In relation to the gross extent of the disease the value of x-ray therapy should be demonstrated best in those patients whose tumors were partly or altogether inoperable. Six such patients are living for five or more years, although the significance of this is mitigated by the fact that in four of these the tumors were of Grade I malignancy. One of the others now has a recurrence, and the other is apparently free of malignancy after nine and one-half years. To compare the duration of life in the patients who received x-ray therapy with those who did not would give an inaccurate impression of the value of the x-ray, since in most instances those who were not so treated had metastasis to the liver or were too ill to tolerate the treatment. All of these died within one year, most of them within six months. Among fourteen patients with partly operable tumors of Grade II and Grade III malignancy who have died following x-ray therapy, three lived for six months; one for eight months; three for one and one-half years; one for one and two-thirds years; one for one and three-fourths years; one for two and one-half years; and four for three years. Of thirteen with inoperable tumors who died following x-ray therapy, four lived less than three months; four lived for six to twelve months; two for one and one-half years; one for one and two-thirds years; one for three years; and one is untraced. It would appear that the x-ray probably prolonged the life of some of these patients.

Our experience with x-ray therapy in pseudomucinous tumors where the growth was partly or completely inoperable is limited to three patients. One of these who had a partial operation survived for six and one-half years, and another for one and one-half years, while one whose growth was inoperable lived three years, during which time she had x-ray therapy on two occasions. However, there is some question as to whether this would be regarded as a pseudomyxoma peritonei. In considering the serous tumors, if we eliminate all those of Grade I malignancy and all whose tumors were completely removed, we have left twenty-six patients in whom the effect of x-ray therapy might be evaluated. As pointed out above, the x-ray probably prolonged the life of some of these patients. However, only three of this group are alive, and one of these has a recurrence after seven years. One is living four years and the other nine and one-half years without evidence of malignancy. The latter had bilateral tumors limited to the pelvis but not completely operable. In all other patients with serous tumors who are living more than five years without evidence of disease, the growth was either completely removed or the tumor was of Grade I malignancy.

Summary of Results

Table IX presents a summary of the end results in the 107 cases of malignant ovarian tumors. The five-year survival of 44 per cent in the granulosa cell group is influenced by the three untraced cases which are counted as dead. However, the 22 per cent of five-year survivors in the entire group approximates the 20.5 per cent of survivors in the primary adenocarcinoma group.

We agree with Dr. Montgomery that every case should be operated on and as much of the tumor removed as possible. It is interesting that in thirty-five out of eighty-four cases nothing more than exploration was done, for, in the series of 149 cases from the Free Hospital for Women that I reported in 1940, we had been able to remove all or part of the pelvic organs in 141, with a mortality of 6.6 per cent, as against the Jefferson Hospital's 17 per cent. I think this can be accounted for by the fact that our series included many private patients who seek treatment earlier as a rule than those going to outpatient clinics.

Dr. Montgomery's finding that the more solid the tumor is the more malignant it is agrees with other series of cases. Grading these tumors, especially the borderline ones, is a difficult proposition with a large personal equation as was brought out by the discussion in 1940, but in general our results, so far as five-year survivals in the various grades is concerned, corresponds with the readers'. This is also true regarding the greater malignancy of the serous type as compared to the pseudomucinous.

End results are difficult to evaluate, for one can rarely feel sure that the patient is free of tumor, and therefore I believe that five- and ten-year survival figures of all patients are more interesting than those dealing with patients free of disease.

Dr. Montgomery gives 20.5 per cent for the latter classification. If he has the figure for the former I hope he will tell us what it is. There are several reports of 30 per cent to 40 per cent five-year survival, including the 32 per cent at the Free Hospital for Women, but we realize that 10 per cent at least of those survivors have active disease.

We are all interested in the value of radiation treatment. Dr. Malcolm S. Allan is going over our cases again and I am indebted to him for the following figures.

1930 to 1942.—Radiated cases, x-ray alone, 57; radium alone, 3; x-ray and radium, 9; all were operated on first. Forty-one (59 per cent) showed gross metastases. Grade I, 39 per cent; Grade II, 30 per cent; Grade III, 31 per cent. Dead, forty-two (60 per cent) at an average of three and eight-tenths years; alive, twenty-seven (40 per cent) five years or more.

Ten of the twenty-seven cases still living had gross metastases at the time of operation. They have survived five to thirteen years, and one has evident growth.

The 40 per cent survival rate is encouraging, but this is a small series of cases and no conclusions are very valuable.

X-ray treatment, in my experience, does seem to decrease the rapidity with which ascites accumulates.

DR. EDWARD SCHUMANN, Philadelphia, Pa.—Dr. Montgomery's survival figures, as has been said, compare very favorably with others. I must confess to a great deal of skepticism myself regarding survival figures in malignancy. I would like to reaffirm the difficulties of grading these cases and really ascertaining whether or not they are malignant. If we are dealing with the tumor which we have always called cystadenoma, but which we now term endosalpingioma, and which tumors are of Müllerian origin, the lining being of the same pattern and corresponding to that of the Fallopian tube. Necessarily the epithelial lining of these papillary cysts changes with the menstrual cycle of the woman if she be in the menstrual age, and the ordinary skilled pathologist in a hospital has great difficulty in determining whether or not they are malignant. There is a papillary form, an invasive form of this growth, which Dr. Howard Taylor has called semimalignant, and I feel when such tumors occur in any set of figures one doesn't know whether it was ever malignant or not. That is also true of the pseudomucinous cystadenoma where there may well be perineal implants without malignancy. So that I am never convinced that a papillary tumor is malignant, and when we have succeeded in having a survival I do not know whether I have succeeded in curing a carcinoma or merely helped a benign condition.

As to the question of radical operation for a presumably malignant tumor, Dr. Montgomery suggested the Wertheim operation on the side on which the ovarian growth is to be removed. This, I think, is an extremely wise procedure. There also arose the question of the removal of the opposite healthy ovary in a young woman who possesses a papillary cyst of one type or another. Many are convinced that the healthy ovary should not be removed, pend-

one year after supravaginal hysteromyomectomy at which time the ovaries were examined and noted to be normal.

Peritoneoscopy undoubtedly has a place in the diagnosis of ovarian malignancy as noted by Pemberton and by Meigs but unless it is utilized before abdominal distention and persistent pain develop it will be of no avail. In the few cases in which we have used it the symptoms and the physical examination indicated a far-advanced lesion. There is considerable doubt in our minds about the value of this method in early cases, since the ovary is often difficult to visualize if it is not enlarged, especially in obese women. However, in some instances this handicap can be overcome if the procedure is combined with vaginal palpation.

Periodic routine pelvic examination would undoubtedly point the way to earlier diagnosis in many instances. Macfarlane's case illustrates the wisdom of making such an examination at six-month intervals. When some enlargement of the adnexa is noted under such circumstances it may present a difficult problem. In women of childbearing age enlargements of the ovary of approximately 5 or 6 cm. in diameter are most likely physiologic in origin. The prompt operation and radical removal of such ovaries that is sometimes practiced is to be deplored. On the other hand, when such enlargements persist, or show evidence of progressive enlargement, especially in women of menopausal age, an exploratory incision is safer than prolonged watchful waiting. Such a procedure also probably would be wise in certain suspected patients with vague abdominal symptoms, when after thorough study and consultation with an internist no other cause is found for the persistent symptoms.

If malignant disease is to be detected at an early stage in more than an occasional patient, routine periodic pelvic examinations will have to be carried out in large numbers of women and supplemented at times by special studies, and occasionally by an exploratory abdominal incision. The success of such a program will depend upon the ability and care of the family doctor as well as the gynecologist.

The author is indebted to Dr. Theodore P. Eberhardt and Dr. Hugh O'Neil of The Department of Radiotherapy, Jefferson Medical College Hospital, for the data pertaining to x-ray therapy.

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Discussion

DR. FRANK PEMBERTON, BOSTON, MASS.—The symptomatology of this disease is of little value in diagnosis, for it is usually so advanced when seen as to be unmistakable. However, if a patient at or after the climacteric complains of a feeling of pressure in the pelvis and rectum and has no palpable masses, but does have some tenderness in the posterior cul-de-sac, we always think of the everted papillary ovarian carcinoma which has spread to the peritoneum early.

ADVANCED ECTOPIC PREGNANCY

With a Report of Three Cases*

KARL M. WILSON, M.D., WARD L. EKAS, M.D., AND
JOHN H. SCHULTZ, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology of the University of Rochester)

THE great majority of ectopic pregnancies occur within some portion of the Fallopian tube. After a relatively short period of development, their usual fate is either tubal abortion or tubal rupture, with death of the ovum and symptoms of varying severity so far as the woman is concerned. Only under very unusual circumstances will the pregnancy continue to develop so far as mid-pregnancy, and still less frequently is it possible for the pregnancy to proceed to term. Schumann cites the very unusual case reported by Conaway in which the pregnancy proceeded to term while still confined within the tube. An interstitial pregnancy on account of its protected location may develop to a considerable extent before it either ruptures or extends into the uterine cavity, becoming a uterointerstitial pregnancy. More often an advanced ectopic pregnancy represents a tuboabdominal, tuboovarian, intraligamentary, or secondary abdominal pregnancy.

Whether a primary abdominal pregnancy is possible has been a much disputed point, but a recent case reported by Studdiford would seem to fulfill the criteria for such a condition.

Inasmuch as advanced ectopic pregnancy, that is, one extending beyond the fifth month, is an infrequent occurrence, no one individual has the opportunity of seeing a large number of cases. An unusually large series is that of Beacham and Beacham comprising twenty cases from the Charity Hospital in New Orleans.

Among the less frequently observed types of advanced ectopic pregnancy are those that develop secondarily between the folds of the broad ligament. In order for such an occurrence to take place, a rather unusual set of circumstances would be necessary. The ovum would first be implanted in the tube on its lower side, that is, adjacent to the mesosalpinx. After a limited period of development, erosion of the tube wall occurs in such a manner as to permit extrusion of the ovum into the space between the folds of the broad ligament on the involved side. Usually such an accident will result in the death of the ovum and the development of a broad ligament hematoma, but if an area of the chorion sufficient for the nutrition of the ovum remains attached to the tube, its further growth may occur. In association with this growth, further chorionic attachments will be acquired on one or both leaves of the broad ligament, the parametrium, or the lateral wall of the uterus. Such a secondary intraligamentous pregnancy may continue to develop for a considerable period of time, and may

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ing a most careful pathologic examination of the specimen. This cannot be carried out quickly so that it becomes obligatory to subject the patient to another operation if the ovarian tumor is found to be malignant.

DR. ARTHUR H. CURTIS, Chicago, Ill.—It just occurred to me that you may be interested in the story of a patient of Dr. Watkins' and myself. When we opened the abdomen it looked like a very hopeless affair, implants from a solid ovarian growth spread throughout the abdomen, associated with ascites. We removed every thing available, as was a little unusual for us to do in those earlier days. The patient lived very satisfactorily for ten years. Then she had a recurrence and we removed again as thoroughly as possible. She lived for another five years and then died of malignancy. It shows we should never give up.

DR. CURTIS F. BURNAM, Baltimore, Md.—I agree fully that x-ray is not of a great deal of use in treating carcinomas of the ovary, but there seems to be some exceptions. I had a case referred to me by one of Baltimore's gynecologists where he had removed a solid carcinoma of the ovary. For a year and one-half this patient seemed quite well, and then she developed a mass in the cul-de-sac, a hard, fixed mass. An exploratory operation was done. We made a diagnosis of recurrent carcinoma but no specimen was taken at the last operation. That patient was treated by x-ray. The lesion cleared up and there has been no return in eight years.

DR. MONTGOMERY (Closing).—I think our series includes an unusually high percentage of hopelessly inoperable patients. Twenty-eight of the entire group were treated on the private service.

The figure of 20.5 per cent to which Dr. Pemberton referred is based upon the sixty-eight cases available for five-year study. Twenty and five-tenths per cent of these are living and have no evidence of recurrence of their carcinoma at present.

Dr. Schumann mentioned the endosalpingioma described by Barzilai. Those tumors that we have classified as of low grade malignancy would probably be included in that group.

Radical surgery, when it can be done completely and safely, is undoubtedly the best treatment for the patient with carcinoma of the ovary. There is only one survivor in our group with actively malignant tumors where the growth was not completely removed. That patient received postoperative x-ray therapy and has remained well and free from any evidence of carcinoma for ten years. All others who have survived for five or more years had tumors that were either completely removable or of low grade malignancy.

In our experience, x-ray therapy has been a valuable adjunct in the treatment of these patients. It frequently prolongs life, but seldom is responsible for complete survival.

period had occurred on March 8, 1944, and the estimated date of confinement was Dec. 15, 1944. No history of any unusual events in connection with the pregnancy was elicited at this time and she was registered as a normal pregnancy of about seven months' duration, the fundus being described as four finger-breadths above the umbilicus.

A month later she was admitted to the hospital with the complaint of intermittent abdominal pain, only moderately severe, with no bleeding. The symptoms subsided in a couple of days and she was discharged as representing a supposed threatened premature labor. No fetal heart sounds were heard, but x-ray revealed a normal near-term fetus presenting by the vertex with no overlapping of the skull bones.

She was readmitted on Nov. 24, 1944, after an attack of very severe abdominal pain. On admission the general condition was good, blood pressure, 128/90; temperature, 37° C.; pulse, 100; red blood cells, 3,390,000; white blood cells, 8,950; hemoglobin, 10.5 grams. She complained of intense abdominal pain. There was some abdominal distention and rather marked tenderness, especially on the right, and the fetal parts were outlined with unusual ease. Fetal heart sounds were readily heard. Examination under anesthesia revealed the fetal head at the level of the spines with an apparently very thin layer of tissue covering it, while the cervix was discovered high up at the upper level of the symphysis. It was of soft consistency and closed. At the previous examination in O.P.D. and at the previous admission the cervix was in its normal location. There was no bleeding. The most probable diagnosis appeared to be sacculization of the uterus with rupture, though some consideration was given to the possibility of an advanced ectopic pregnancy. Operation was undertaken at once. On opening the abdomen, a living near-term fetus was first encountered and was easily extracted. Amniotic fluid was present in the peritoneal cavity, but there was no free blood. Exploration of the pelvis revealed a uterus enlarged to about the size of a three and one-half months' pregnancy lying somewhat to the left of the midline. To the right of this was the sac which contained the pregnancy, and this was identified as the distorted right broad ligament. In its posterior leaf was a jagged rent about 12 cm. in length representing the rupture through which the fetus had escaped (Fig. 1).

The placenta, about the usual size of a full-term placenta, was found attached to the anterior sheath of the broad ligament and to the right of the lateral wall of the uterus. There was no evidence of placental separation. The right ovary appeared normal, while the right tube which presented an open fimbriated end was found to be intact for a distance of about 6 cm., at which point it entered the sac of the pregnancy. Obviously under the circumstances present, no attempt could safely be made to remove the placenta. Repair of the rent leaving the placenta in situ to undergo resorption was considered, but unfortunately, during our manipulations in the exploration of the pelvis, the anterior sheath of the sac was torn, and this resulted in such severe bleeding that the only logical procedure appeared to be to remove the sac together with the uterus as rapidly as possible. This was accordingly done, the uterus being amputated supravaginally and both appendages retained. Removal of the uterus was necessary on account of the attachment of the placenta to its right lateral wall. A transfusion of 1000 c.c. of whole blood was begun during the operation. Her convalescence was uneventful. The baby weighed 2,790 Gm. and did well. The head showed some pressure asymmetry which did not disappear for several weeks. Close questioning after the operation brought out a significant item of history. A little over two weeks after her menstrual period in March, she had an episode of sudden sharp right lower quadrant pain associated with slight vaginal bleeding. A similar but less severe attack occurred in May. This additional history permits a reasonable reconstruction of the course of events. It

even go to full term. At the same time there is always the possibility of a secondary rupture of the sac containing the pregnancy into the peritoneal cavity. If no rupture occurs or if it is not removed, the ovum will perish and may be retained in situ for an indefinite period, even many years, and eventually possibly result in a lithopedion formation.

Also, among the less frequently encountered types of advanced ectopic pregnancies are those occurring in a rudimentary uterine horn. Such pregnancies are, of course, technically not extrauterine pregnancies, but are included as the broader term "ectopic," as would be also the rare cervical pregnancy.

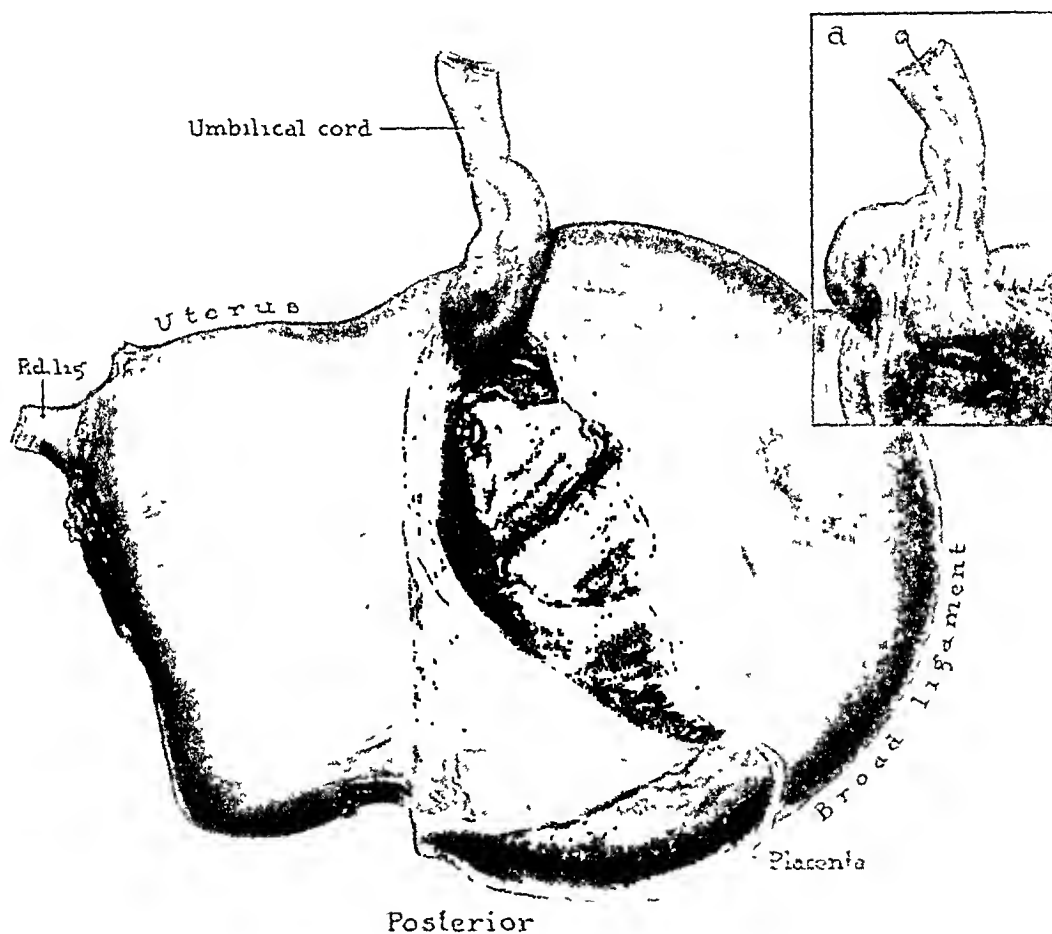


Fig. 1.—The ruptured sac of the full-term broad ligament pregnancy of Case 1. The placenta is still in situ, the rupture being through the posterior wall of the broad ligament. Note in inset the velamentous insertion of the cord, indicating the original site of implantation of the ovum.

How far a pregnancy in a rudimentary horn will proceed will, of course, depend on the size of the horn and the degree of hypertrophy of which it is capable. In our material of 195 various types of ectopic pregnancies, three can be classified as being in the advanced group, two were of the intraligamentary type, and one was a pregnancy occurring in a rudimentary horn.

CASE 1.—M. de H., No. 223668, aged 25 years, white, para i. The patient had had one full-term spontaneous delivery five years previously, and one miscarriage in 1941. Otherwise her past history was irrelevant. In her present pregnancy, she was first seen in the O.P.D. on Oct. 4, 1944. Her last menstrual

was re-established in October, 1945, and continued regularly and normally from that time on. She was admitted to Strong Memorial Hospital on Nov. 20, 1946, after having just finished a menstrual period. The time of admission represented twenty-three months after the probable beginning of the pregnancy, and seventeen months after the probable death of the fetus. From September, 1945, to October, 1946, she gained in weight from 157 pounds to 187 pounds.

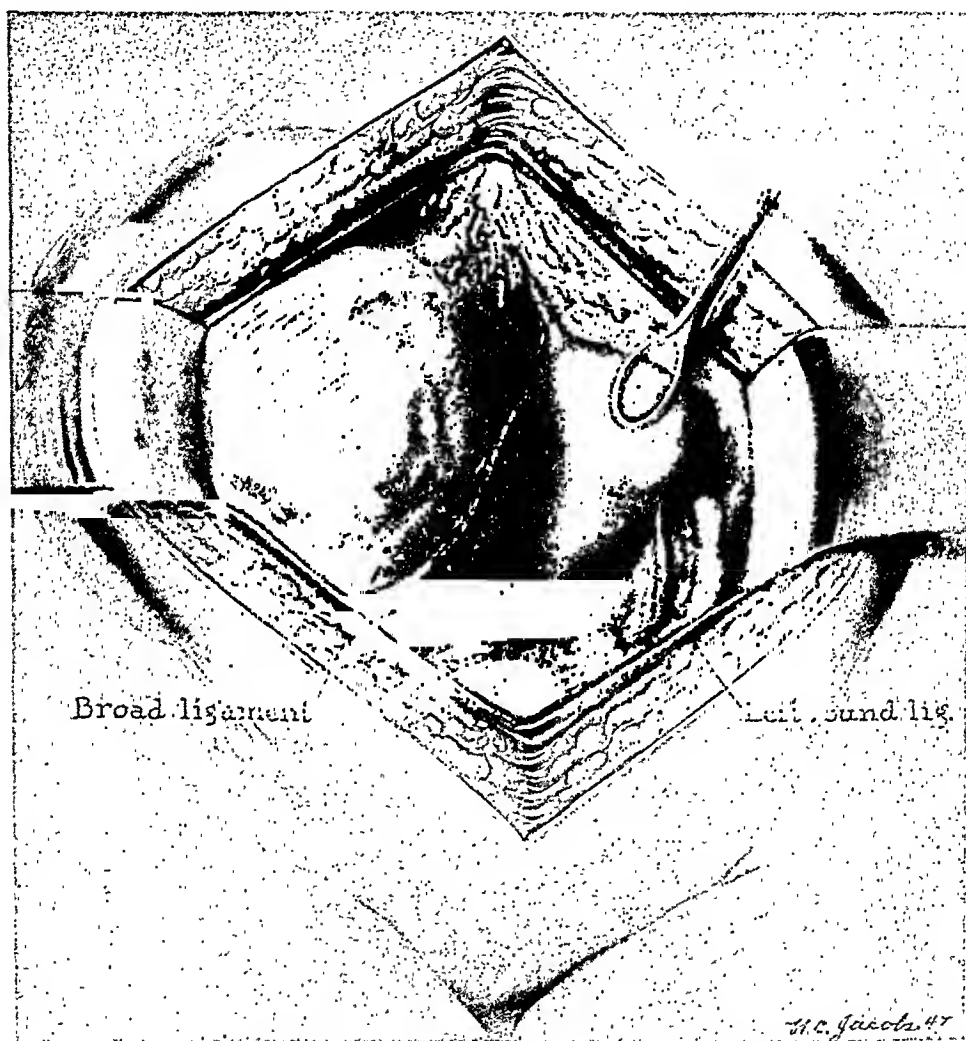


Fig. 3.—The right broad ligament pregnancy in Case 2 after the abdomen was opened.

Examination on admission showed the following pertinent facts: blood pressure, 115/75; temperature, 37; pulse, 72; red blood cells, 4,950,000; white blood cells, 6,600; hemoglobin, 14.0 grams. A mass was felt rising from the pelvis and extending up to the level of the umbilicus. This was rather soft in consistency, nonsensitive, and no fetal parts could be outlined and no fetal heart sounds heard. The Friedman test was negative, and x-ray revealed an obviously dead fetus of about five months' development (Fig. 2).

Pelvic examination revealed the following findings: Outlet: Nulliparous, healthy, no bleeding. Cervix: Small, firm, closed. Uterus: Normal size and displaced posteriorly and to the left. Appendages: On the right was a rather soft mass about 18 cm. in diameter corresponding to the mass felt on abdominal examination. Left appendages were not outlined.

seems probable that this pregnancy began as one in the isthmic portion of the tube. Partial rupture probably occurred at the time of her first attack of pain and bleeding, and possibly further rupture between the folds of the broad ligament occurred at the time of her second attack in May. Further evidence as to the original site of implantation is to be found in the presence of a velamentous insertion of the cord at this point.

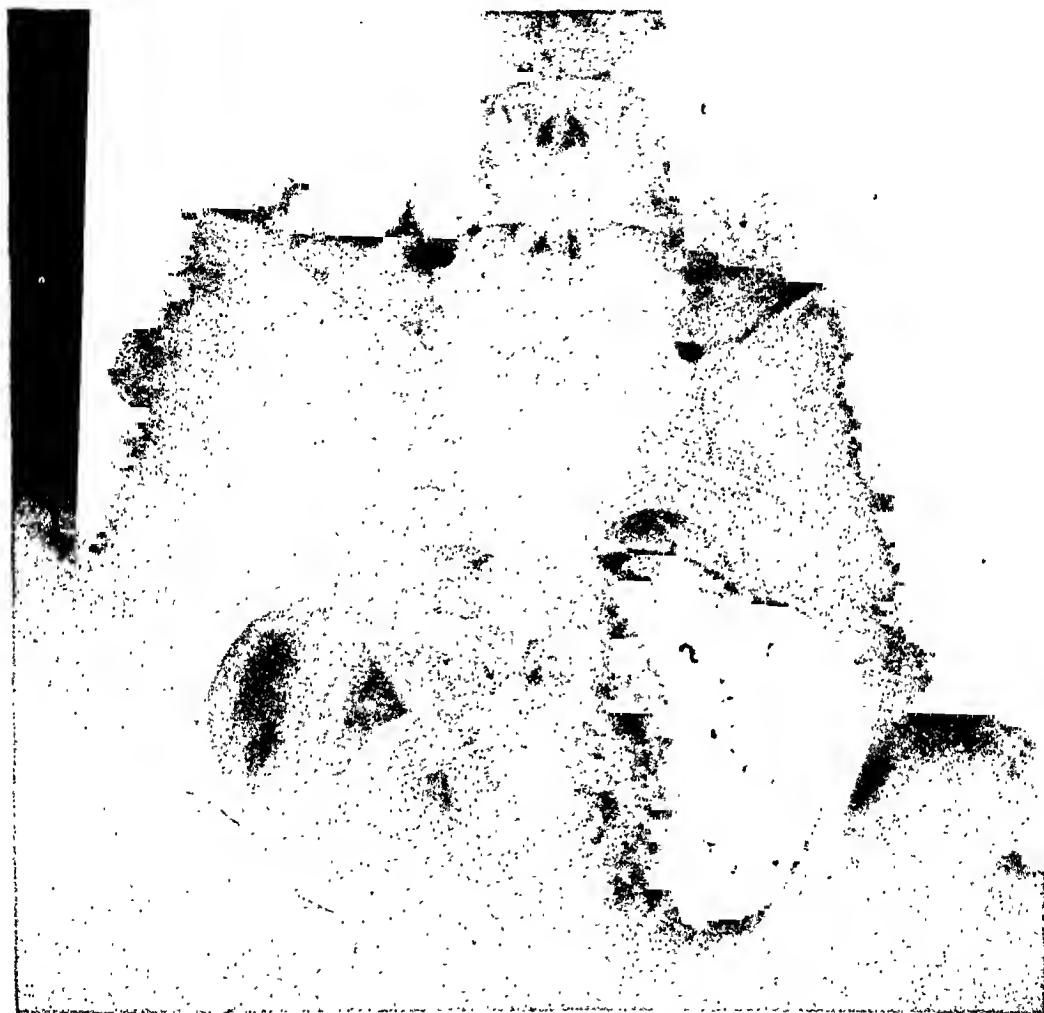


Fig. 2.—Preoperative x-ray showing dead fetus in Case 2.

CASE 2.—M. H., No. 19107, aged 26 years. The patient's past history was irrelevant. In her present pregnancy, the last menstrual period had occurred on Jan. 1, 1945, the expected date of confinement being Oct. 8, 1945. Fetal movements were first noticed in April. Up to May, 1945, the pregnancy was quite uneventful, but at that time an episode of slight vaginal bleeding and abdominal cramps occurred which subsided after rest in bed. Her doctor took her to another hospital in late July, 1945, on account of some vaginal bleeding but with no pain. An x-ray at that time showed a fetal skeleton of about six months. No fetal movements had been noted for a week previous. The fetal heart sounds were not heard. A diagnosis of threatened abortion was made. Six months later, in late January, 1946, her doctor readmitted her to the same hospital for twenty-four hours' observation with a diagnosis of false labor. In May, 1946, an x-ray showed definite evidence of a dead fetus. Menstruation

nancy into the broad ligament occurred. Careful questioning brought out no history of pain or bleeding prior to the fifth month, yet it seems unlikely that rupture occurred at that time with the minimal symptoms she then presented, and considering the degree of development of the pregnancy at that time. This represents, too, a situation in which it would seem perfectly possible for a uterine pregnancy to have occurred in conjunction with the other after menstruation had been re-established.

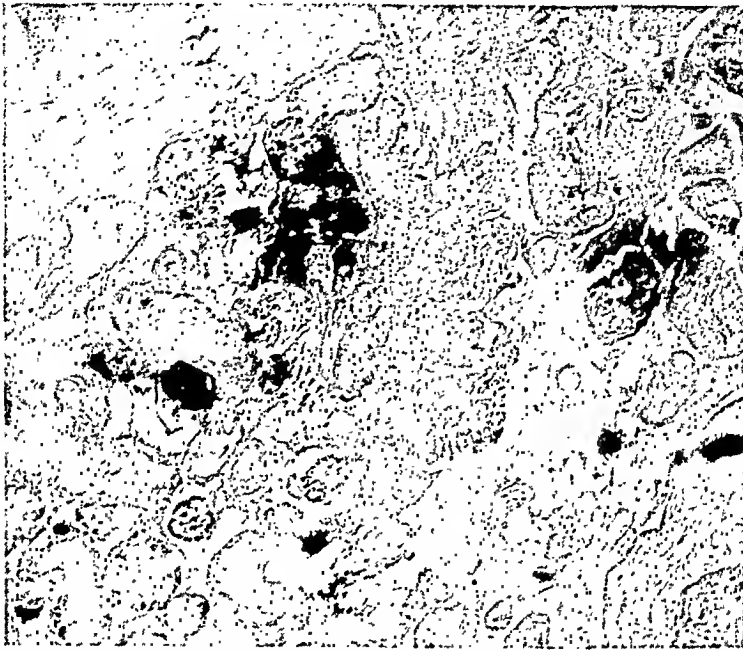


Fig. 5.—Hyalinized placental villi with some calcium deposits from Case 2.

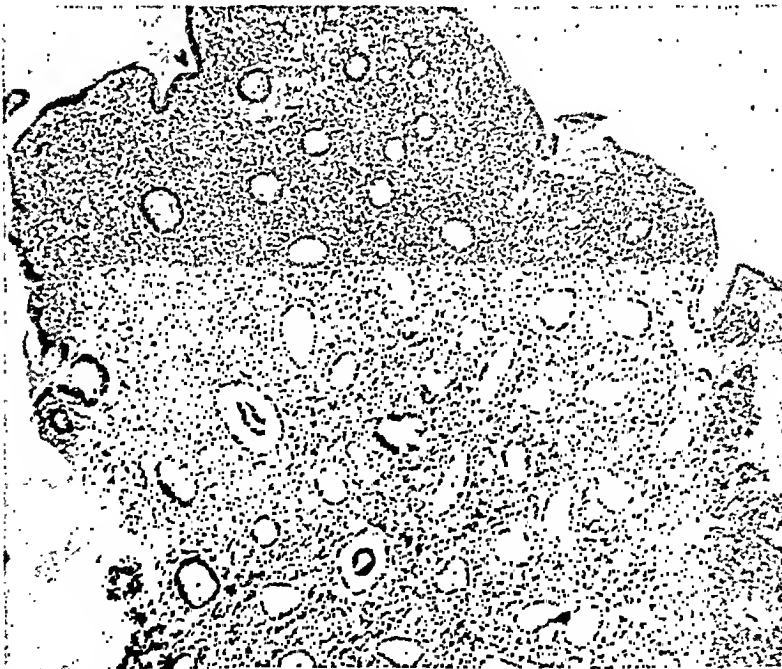


Fig. 6.—The normal postmenstrual curettings obtained from Case 2.

Diagnosis: Extrauterine pregnancy of about five months, with dead fetus.

Operation: A curettage was done in order to obtain some endometrium for study. Laparotomy was then proceeded with. On opening the abdomen no old or recent blood was found in the peritoneum, but a few adhesions were encountered on the right side and were released. The pregnancy was found to be between the folds of the right broad ligament, and the right tube was observed coursing over it (Fig. 3).



Fig. 4.—The mummified but not calcified fetus removed from Case 2.

While freeing adhesions the posterior leaf of the sac was broken open. The mummified fetus was extracted, and the fibrosed placenta was easily peeled off and removed. There was no bleeding. The right tube and some redundant broad ligament tissue were removed, the right ovary being retained and attached near the uterine cornu. The left appendages were quite normal and were retained. Closure of the pelvic and abdominal wounds was completed, silk sutures being used throughout. Her convalescence was uneventful. The mummified fetus weighed 375 Gm. Its crown-rump length was 16.5 cm., the over-all length 32 cm. (See Fig. 4).

The placenta was a well-defined organ measuring 7 by 9 cm., but microscopically the tissue was found to be markedly hyalinized and degenerated with occasional shadow villi to be identified (Fig. 5).

It contained some calcium deposits and numerous phagocytes. Microscopic examination of the tube removed showed chronic salpingitis. The curettings showed early interval endometrium (Fig. 6).

It is interesting to note that no evidence of breast activity was noted post-operatively. One can only speculate as to the time that rupture of the preg-

tion was made. In a few hours, however, the whole picture changed and she went into profound shock with all the signs of acute internal hemorrhage. Immediate operation was arranged for, a transfusion of whole blood being begun at the time the operation was begun.

On opening the abdomen at least 1,500 c.c. of fresh blood was found in the peritoneal cavity. A fetal sac of between five and six months' gestation was found free in the peritoneal cavity with a portion of the placenta adherent to a jagged wound, about 8 cm. in diameter, which at first sight appeared to be in the fundus of the uterus. Further exploration, however, revealed that the wound was in a rudimentary uterine horn attached to the right side of a slightly enlarged uterus (Fig. 7).

Its pedicle was narrow, only about 2 cm. in diameter. After removal of the fetal sac and placenta no communication between the rudimentary horn and the uterus could be demonstrated. Both appendages appeared quite normal. The pedicle of the rudimentary horn was ligated and cut, the right appendages were dissected free from it and preserved, being attached to the right uterine cornu.

These areas were covered and the abdomen closed. Silk sutures were used throughout. After completing a transfusion of 1,000 c.c., she responded quickly and had an uneventful convalescence. The fetus weighed 600 grams.

Summary and Discussion

Three examples of advanced ectopic pregnancy are presented, two of the intraligamentary type, and one a pregnancy in a rudimentary horn. One of the former went to term and a living child was delivered at operation, while in the second one the fetus died in situ and was retained for seventeen months before operation was carried out. The third case represented an acute rupture of a five to six months' pregnancy in a rudimentary uterine horn. All of the patients made uneventful recoveries after operation.

In all advanced ectopic pregnancies difficult diagnostic problems may arise. Often they may be overlooked simply because they occur so infrequently that the average person is likely to forget they occur at all. When the patient is first seen late in pregnancy, unless the examiner discovers the slightly enlarged uterus at one side of the fetal sac, he is likely to regard the situation as a normal pregnancy on casual examination. Even if the uterus itself is found, it may be mistaken for a subserous myoma attached to the side of the supposed full-term pregnant uterus. Absence of contractions in the large sac is a diagnostic point of value if the pregnancy is extrauterine, while palpation of the round ligaments in symmetrical relationship to an abdominal mass would indicate that the mass is the enlarged uterus. Death of the advanced fetus with retention might on occasion suggest an ovarian tumor, especially when the small uterus is demonstrated apart from the mass. X-ray picture would provide the answer to the problem. The treatment is, of course, always surgical. The operation performed may be a very simple one on occasion; nothing could have been easier, for example, than the operation carried out in our Case 2. On the other hand, the operation may be an extremely difficult and hazardous one. The difficulties and dangers will depend largely on the relationship which the placenta may have acquired in regard to other structures. Secondary rupture of the sac as occasionally occurs may represent an acute surgical emergency with severe intraperitoneal hemorrhage. The mode of handling the placenta at the time of

CASE 3.—R. D., No. 247708, aged 18 years. Her past history was irrelevant.

Present Pregnancy.—She was first seen in O.P.D. on May 8, 1946. Her last menstrual period occurred on Nov. 4, 1945, with a scanty two-day flow on Dec. 4, 1945. Her expected date of confinement thus was either Aug. 11, 1946, or Sept. 11, 1946. Examination revealed a mass rising from the pelvis and extending up to the umbilicus. It was described as being rather firmer and less globular than the normal pregnant uterus. No other findings of significance were discovered, and the situation was regarded as a normal pregnancy of between

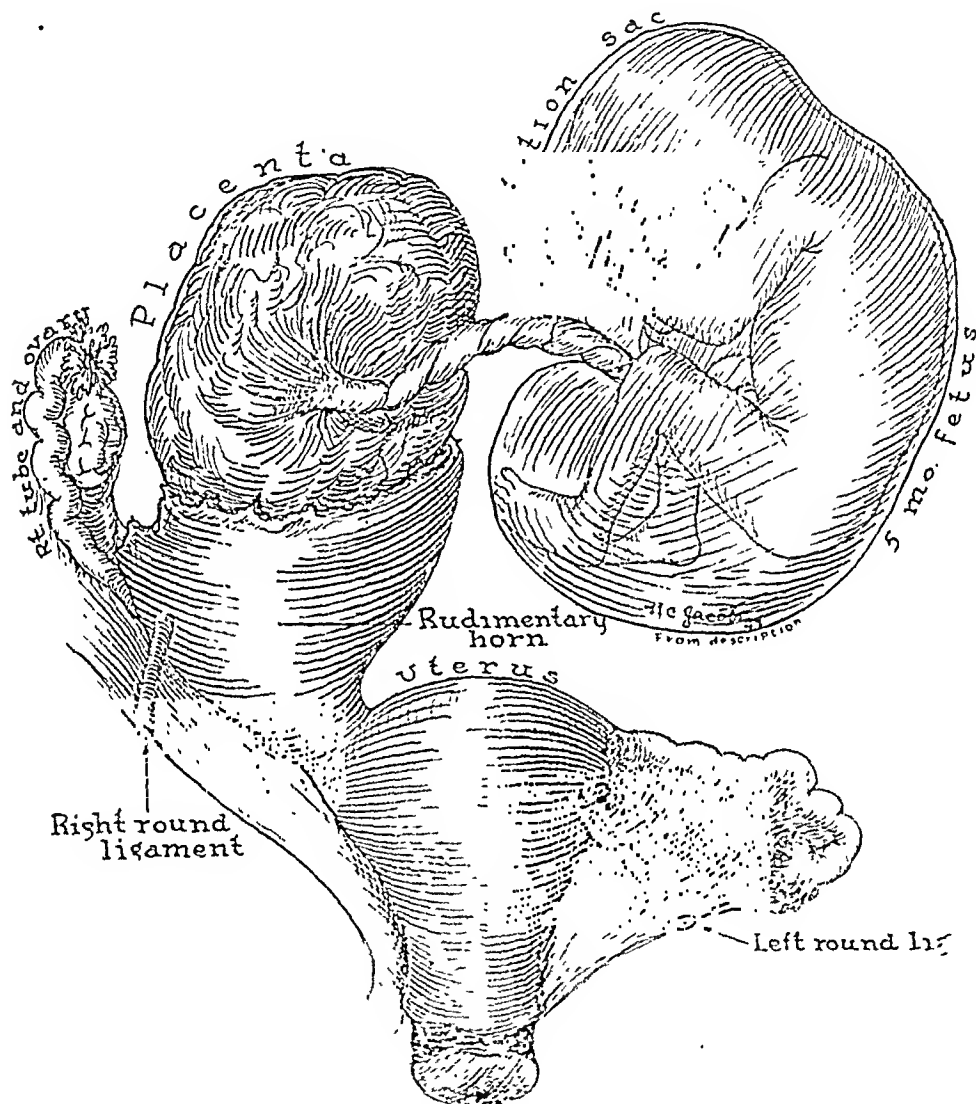


Fig. 7.—Diagram of the findings at operation in Case 3, with complete rupture of the rudimentary uterine horn on the right.

five and six months' duration. She was admitted to the hospital ten days later with the complaint of crampy lower abdominal pain and vomiting, but no bleeding. Admission temperature, 36.9° C.; blood pressure, 112/65; red blood cells, 3,100,000; hemoglobin, 12 Gm.; white blood cells, 10,500. There were para-umbilical pain and dysuria with frequency. The urine showed a trace of albumin, and the sediment was loaded with white blood cells and epithelial cells. The uterus could not be differentiated from the mass felt on abdominal palpation. X-ray examination showed a normal fetus of from five to six months' development. A tentative diagnosis of pregnancy with associated urinary infec-

posterior surface of the right broad ligament, except at one area along the outer border where it was still lightly attached. The placenta was removed without difficulty, and there was no fresh bleeding. One and one-half liters of free blood were siphoned off, and on further inspection there was some fresh bleeding from the area along the outer border of the right broad ligament. This segment was clamped, cut, and ligated, after which there was no further bleeding. The abdomen was closed with through-and-through heavy black silk sutures, the skin with clips. The infant, a male about thirty weeks old, weighed 1,120 Gm. and died forty minutes after delivery, having breathed only a few times during this interval. At the completion of the operation a second transfusion was given. Convalescence was uneventful, and she left the hospital Aug. 27, 1942, sixteen days after operation.

Dr. Wilson has called your attention to the importance of history. I can only emphasize this point and say it is most important. After a complete physical examination a flat antero-posterior x-ray film will usually clinch the diagnosis. If the nonpregnant uterus can be palpated, or if the fetus is dead, as shown by the x-ray, hystrogram would prove extrauterine gestation. The Aschheim-Zondek or Friedman test is of unquestionable value.

As to the time of operation, we believe that the operation should be performed as soon as the diagnosis is made, except where the diagnosis is not made until late in pregnancy and there is a question of a viable fetus. In such an instance operation may be deferred until the thirty-sixth or thirty-eighth week, provided the patient is kept under constant observation, preferably in the hospital.

The management of the placenta is most important. Realizing, as pointed out by Wharton, that the life cycle of an abdominal or advanced ectopic pregnancy is abnormal, and that the placenta with its "trophoblastic activity becomes attached to and attacks any structure with which it comes in contact," it would seem wise to leave the placenta in situ, after ligating and cutting the cord flush with the fetal surface. The abdomen is closed without drainage. It requires very little "tugging or inspection" to start uncontrollable hemorrhage. Besides, there is little or no danger in leaving the placenta "where you find it." Of course, if there is a distinct pedicle to the placental attachment which may obviously be securely ligated, or where the fetus has been dead long enough to allow of complete "death of placenta," it may be removed without fear of bleeding. In the presence of frank infection the placenta is left in situ and drainage should be instituted through the lower end of the abdominal wound. Marsupialization is not recommended, except where there seems no other way out.

In conclusion, we suggest that the maternal morbidity and mortality could be materially lowered by: (1) early diagnosis and prompt operation; and (2) better surgical judgment in the management of the placenta.

DR. ARCHIBALD CAMPBELL, Montreal, Quebec (By Invitation).—Dr. Wilson is to be congratulated on his having saved all the patients in his series, and on obtaining a living child in the only one in which this was possible. I thoroughly agree with Dr. Wilson that we are all inclined to be too casual in our history-taking of the pregnant patient.

Since 1930, there were 224 early, extrauterine pregnancies encountered at the Royal Victoria Hospital, and over the same period, 162 at the Montreal General Hospital, making a total of 386, of which four were late abdominal pregnancies. During the same period, there were 36,480 confinements. From this small series it would therefore seem that ectopic gestation occurs once to every 100 confinements, and that of all extrauterine pregnancies, approximately 1 per cent reach the stage of viability.

Of the four cases at the Royal Victoria Hospital similar to those reported, the fetus was macerated or dead before coming under observation in three of the cases. In one case, the condition being recognized, the late Dr. H. C. Burgess performed a laparotomy, delivering a living baby. In none of the cases was an attempt made to remove the placenta completely, but rather only a part of the redundant tissue. One patient died of septicemia.

No doubt, in a certain number of instances, patients with extrauterine pregnancy, early or late, recover spontaneously either by a process of absorption, mummification, or extrusion of the fetal parts into the vagina, bladder, or rectum. In this connection, the late Dr. H. M.

the operation is of the greatest importance. When the fetus is still living, or if very recently dead at the time of operation, any separation of the placenta even over a small area will probably be attended by profuse and possible uncontrollable hemorrhage. This was vividly demonstrated to us in our Case 1. In this type of case it is usually preferable not to attempt to remove the placenta, but rather to allow it to remain in situ, and eventually it will undergo resorption. In an intraligamentary pregnancy, however, it may be feasible to remove the whole sac containing the placenta, preserving the uterus if possible. When the fetus has been dead for some time the placental circulation will no longer be active, and the placenta can usually be safely separated from its attachments and removed, but, again, if this proves too difficult, it may be left to undergo resorption. Marsupialization of the sac may on occasion be considered, attaching the edges of the sac to the abdominal wound, in which event the placenta may later separate and be extruded through the opening, either complete or in fragments. We have had no experience with the procedure. It would appear to have a very limited application, but might possibly be considered if infection were already present.

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Discussion

DR. HARVEY MATTHEWS, Brooklyn, N. Y.—Dr. Wilson has forcefully called our attention to a very rare but important subject. We have had only four cases in our service at the Long Island College Hospital during the past thirty-five years. This substantiates the fact that advanced ectopic pregnancy (20 weeks or more) is of rare occurrence. In addition to these cases, I have seen in consultation at another hospital one other case of full-term abdominal pregnancy. This baby was delivered at full term weighing 9 pounds, is living and well fifteen years after operation.

CASE REPORT.—Mrs. R. M., Negro, aged 37 years, para 0, gravida 0, admitted to Long Island College Hospital Aug. 11, 1942, on the service of Dr. George W. Phelan, by whose kind permission I am able to report this case. Family, personal, and menstrual history was irrelevant. She did not know when she last menstruated. Present illness began Feb. 27, 1942, when she began to bleed from the vagina, using three to ten napkins a day and accompanied by constant pain over the lower abdomen. The bleeding ("spotting") continued at irregular intervals through May 28, 1942. The patient, however, continued to work. On June 15, 1942, vaginal bleeding occurred again; and, for the first time, she sought medical advice. Upon examination her physician suspected abdominal pregnancy. On July 15, 1942, the abdomen was x-rayed, and a fetal skeleton outside the uterus was observed. The fetus was apparently alive, lying high up out of the pelvis. On Aug. 11, 1942, because of constant abdominal pain, the physician referred the patient to the Long Island College Hospital with the diagnosis of abdominal pregnancy. Upon admission this diagnosis was confirmed, and shortly following the vaginal examination the patient went into severe shock. The blood pressure was 50/28 and pulse 152, thready, and weak. After treatment with morphine, plasma, blood transfusion, etc., the patient was operated upon under local 1 per cent novocain, supplemented with gas-oxygen anesthesia. Upon opening the abdomen a seven months' living infant, lying free in the abdominal cavity—the sac having been ruptured presumably by the examination—was easily extracted. The placenta was found to have separated from its attachment to the

on the parietal peritoneum, without any decidual reaction, and yet maintain a sufficient blood supply for the maintenance of fetal circulation.

On two occasions I have had the opportunity of removing a biopsy specimen from the placental site. Usually the placenta is firmly adherent, and one hesitates to remove it to obtain the subplacental areas. In these two cases, there was an enormous number of blood vessels but no evidence of decidual reaction at all as one would expect. I believe, however, that this knowledge is still so fragmentary regarding this problem that whenever possible one should observe the placental site in abdominal pregnancy.

DR. SUBODH MITRA, Calcutta, India.—I made some observations on secondary abdominal pregnancy about nine years ago, and reviewing the world literature I found about 411 cases of advanced ectopic pregnancy, to which I have added nine of my own cases. Some of my cases are very interesting. My first patient was 55 years old and she came to me with a history of vaginal bleeding. I found along with cancer of the cervix, a big tumor in the abdomen, which was discovered to be secondary ectopic pregnancy. She had carried this tumor for the last twenty-five years, and subsequently conceived three times, giving birth each time to a normal child. I did not operate upon that patient, the reason being that when she had carried it for twenty-five years, she could as well carry it for the rest of her life.

The second case was important because of advanced abdominal pregnancy occurring twice successively. I was lucky to make the correct diagnosis at the very first consultation, and she was well after operation. About two years later she conceived again and it was also an advanced ectopic. This time she was in one of the district hospitals where, strangely enough, she was operated upon by a doctor who was one of my assistants and who helped me in my operation on this particular patient. The abdomen was opened, a child obtained, but unfortunately the patient died after this second operation.

My third patient was interesting in the sense that she was diagnosed as one of retroverted fixed gravid uterus of five months' duration. The cervix was found pretty high up and the uterus pressing upon the pouch of Douglas. Upon further examination under anesthesia, a ruptured tube was diagnosed and a fetus of four months' duration was removed by laparotomy.

Sometimes it is very difficult to diagnose these cases of secondary abnormal pregnancy. In the literature I find that in about 33 per cent of cases it was not diagnosed at first examination. In the patients where I had difficulty in the diagnosis, some were at term or near term. They were admitted with complaints of acute pain. Questions arose whether it was due to a twisted ovarian tumor, an acute appendix, or a case of accidental hemorrhage. Many cases were diagnosed only after repeated examinations.

There are several important points in making a correct diagnosis, namely, easily palpable fetus by palpation, cervix found high up behind the symphysis pubis, and an indefinite mass in the pouch of Douglas by vaginal examination.

In regard to the management of these cases, I believe the less one interferes with the placenta the better, because it is difficult to remove in most cases. In some, of course, it is easily detachable. As a matter of fact, in one of my cases the placenta was so firmly attached to the sigmoid colon that I had to resect part of the colon. Since then I have decided not to tackle the placenta but to leave it as it is.

DR. WILSON (Closing).—Dr. Campbell mentioned the incidence of advanced ectopic pregnancy. Ours roughly correspond to his. We have had 198 ectopics and three of these were of the advanced type, also there were three ovarian pregnancies.

Regarding the sedimentation rate, that of course is not a specific reaction. It should not differ with ectopic as compared with normal pregnancy unless there has been some hemorrhagic reaction.

With regard to the advisability of operating or not in the advanced cases with living fetuses, personally I would urge immediate operation because of possible secondary rupture, as was true in our first case.

I have had no experience with marsupialization. On the other hand, perhaps it might have a place where the patient already has infection in the sac.

Little, in 1924, operated upon a patient in the Montreal General Hospital for ruptured early, acute left-sided tubal pregnancy. On exploring the pelvis at the time of operation, he encountered a large mass filling the entire pelvis. On further investigation, he found that the mass was composed largely of fetal bones. Included were the skull, ribs, mandible, and femur. The pathologist reported bilateral extrauterine pregnancy, left recently ruptured early, right—late abdominal pregnancy and estimated these bones to be those of a six months' fetus. Reviewing the patient's history, it emerged that some four years previously, when believed by her physician to be five to six months pregnant, the patient suffered from symptoms which, at the time, were interpreted as threatened miscarriage. These symptoms kept the patient an invalid for some three months, when ultimately they disappeared. Menstruation returned and the episode was forgotten.

The diagnosis of extrauterine pregnancy rests largely on history. On examination, the presence or absence of demonstrable uterine contractions, the ease with which one can identify fetal parts; a highly-placed transverse presentation should more than arouse suspicion. In most cases of late abdominal pregnancy, the cervix is located high in the vaginal vault. It would seem that x-rays do not give conclusive information. I should like to ask Dr. Wilson if he feels that the sedimentation rate might not add considerable information in suspected cases.

The problem of extrauterine gestation is particularly serious from an ecclesiastical standpoint. I should like to ask the essayist a question pertinent to this situation:

If one were to recognize a late abdominal pregnancy, unaccompanied by symptoms, in the event of the child being alive, but of questionable viability, should such a case be treated as an emergency, or would one be justified in postponing operation in the hope that by waiting one might obtain a viable baby?

DR. ALFRED BECK, Brooklyn, N. Y.—My interest in this subject was stimulated by the difficulty which Dr. J. O. Polak and I encountered in handling a case of extrauterine pregnancy. As a result of this difficulty I reviewed the literature very carefully, and subsequently wrote a paper on the subject which was read at the meeting of the American Medical Association in 1919. In this paper it was suggested that the placenta be removed whenever the circulation of the placental site could be easily exposed and controlled. Whenever, on the other hand, the circulation could not be exposed, I suggested that the placenta be left within the abdomen and the abdomen closed without drainage.

Subsequently, two of my associates encountered full-term abdominal pregnancies and treated them thus: the placenta was left within the abdomen and closure made without drainage. Both made good recoveries. In one of them the abdomen was opened several years later and no trace of the placenta could be found. After that I followed the literature carefully and have noted that a fairly large number of cases have been treated by leaving the placenta within the abdomen and closing without drainage. Seldom was it necessary to do a subsequent operation.

From my observation in my early study and subsequent observation of the literature, I wish to condemn the last suggestion of Dr. Wilson, namely, marsupialization. It gives the highest mortality of all methods of treatment. Most of the patients so treated died from peritonitis.

In my study the mortality seemed to be least when the operation was done about two weeks before term. A number of men carried their cases in the hospital sometimes as long as a month in order to reach this optimum period, and then operated. Of course, when such expectant treatment is used, the patient should be in the hospital so that an emergency operation can be done if the sac ruptures.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—There is a phase of this subject of secondary abdominal pregnancy which I feel requires far more study and which the Fellows of this Society may bring to a conclusion by careful observation of their cases. I think none of us has observed these secondarily attached placentas without being astonished at the blood supply of the placental implantation. When one sees the well-established blood supply in the abdominal cavity, one is continually surprised to find this organ, four-fifths of which may be

Opinion Concerning the Intrauterine Pack

Review of the literature furnishes ample evidence that the employment of the intrauterine pack for postpartum hemorrhage is a controversial subject.

Cosgrove, Leff, and Hunter indicated that the use of such a pack should be kept to a minimum; they asserted that the postpartum use of uterine tamponade is unphysiologic, that it holds open the uterine sinuses, thus allowing loss of blood to continue, and that the uterus then distends rather than contracts, so that a hemorrhage which otherwise would be revealed is converted into a concealed hemorrhage. These writers said that they employ oxytocic agents and other measures, particularly bimanual compression, in the control of the uterine loss of blood, and that they may even maintain this compression for a prolonged period. Sherrick, Davis, and others^{1, 14, 16, 19, 21} among the obstetricians who write about the management of postpartum hemorrhage, do not mention the use of intrauterine packs. The use of the hot intrauterine douche as a hemostatic measure, before resort to packing, was advised by Corbet and Dupuy; this procedure seems to enjoy especial favor among British authors. The douche employed is carried out with either hot water or hot dilute acetic acid.

A large number of obstetricians, Pastore and Stander, Falls, DeLee, and others^{7, 9, 10, 11, 17, 20, 23} have said that intrauterine tamponade should be used as soon as it becomes evident that postpartum uterine hemorrhage is not being controlled by the usual available measures. These authors asserted that the intrauterine pack acts in two ways to control the bleeding; (1) by actual tamponade, and (2) by serving as a foreign body to stimulate uterine contraction. The authors referred to were in general agreement that, when packing becomes necessary, it should be done without delay.

The type of pack used varies, and many writers have said that this is of great importance. Falls, in 1937, used a pack moistened with a 1 per cent solution of cresol (lysol); DeLee in 1938 recommended use of a pack moistened with an 0.5 per cent solution of cresol (lysol); Soule used plain, iodoform, or sulfanilamide gauze packs. Randall remarked that it is not important to argue about the type of pack to be used, but that it is important, after the decision to pack has been reached, to do it quickly and correctly.

The Present Study

Third Stage of Labor.—We wish to outline briefly the management, in general, of the third or placental expulsion stage of labor which we have followed. This procedure has varied somewhat in the course of nearly thirty years.

Before proceeding with a description of the management of the third stage of labor we should like to mention administration of the extract of the posterior lobe of the pituitary gland as the second stage ends. We have almost never used this extract in the course of labor. The exact time of injection has varied from time to time; usually the extract has been injected directly after delivery of the baby's head or shoulders or entire body. For two years it was the practice to inject the extract immediately after expulsion of the placenta. However, for the greater part of this period it has been customary to inject intramuscularly 1.0 c.c. of alpha-hypophamine (pitocin) during delivery of the head and shoulders of the baby.

Because of the controversial nature of this subject, we feel we should state that in our management of the third stage of labor, we have been mindful of the mechanism of placental separation and expulsion. Also, it may be stated

THE INTRAUTERINE PACK IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE*

LOIS A. DAY, M.D., ROBERT D. MUSSEY, M.D., AND
ROBERT W. DEVOE, M.D., ROCHESTER, MINN.

(From the Section on Obstetrics and Gynecology, Mayo Clinic, and the Mayo Foundation)

CONTROL of postpartum hemorrhage continues to be one of the highly important problems which are encountered by obstetricians. On the presence of postpartum hemorrhage which has not been controlled by oxytocic drugs or by abdominal and sometimes bimanual uterine massage, the use of the intra-uterine iodoform pack or tamponade for many years has been prominent among the active hemostatic measures we have employed.

Deaths Caused by Obstetric Hemorrhage

There has been a striking decrease in the maternal death rate in this country in somewhat more than a decade. This trend is more or less nation-wide. The lowered maternal mortality rate has been caused by sharp reduction in two of the leading causes of maternal deaths; namely, puerperal sepsis and the toxemias. Maternal mortality caused by obstetric hemorrhage, however, has remained practically constant, except for minor fluctuations. For example, vital statistics of the State of Minnesota show that in the year 1934 the maternal deaths from puerperal sepsis, toxemia, and hemorrhage were approximately twenty, eight, and six, respectively, per 10,000 live births. In the year 1940 the number of deaths from sepsis, for the same number of live births, had decreased to nearly five; deaths from toxemias had decreased to a little more than four; but the number of deaths from hemorrhage had not diminished.

No doubt a wider application of the principles of adequate prenatal care, of conservative and aseptic management of labor, and the employment of chemotherapy have been important factors in the lowering of the maternal mortality rate of the toxemias and sepsis. However, these factors, in addition to more advanced obstetric education and an increase in the number of patients hospitalized for obstetric complications, also should have helped lower the incidence of obstetric hemorrhage.

It is not our purpose in this paper to review the whole subject of obstetric hemorrhage. Among the various causes of such hemorrhage, that which occurs post partum is responsible for the largest proportion of maternal deaths from hemorrhage. Analysis of the management in such cases has shown that, although deaths from postpartum hemorrhage are not entirely preventable, under ideal conditions they are almost preventable. Among these ideal conditions are adequate prenatal care, conservative management of labor and its third stage, hemostasis, and the replacement of loss of blood volume.

*Read before the meeting of the American Gynecological Society, Montebello, Quebec, Canada, June 17 to 19, 1947.

TABLE I. INDICATIONS FOR INTRAUTERINE PACKING AMONG 267 WOMEN

CONDITION	PRIMIPARAS	MULTIPARAS	COMBINED
Hemorrhage persisting after delivery of placenta	56	50	106
Hemorrhage persisting after manual removal of placenta	21	25	46
Uterus remaining atonic after manual removal of placenta	27	31	58
Uterus remaining atonic after cessation of postpartum bleeding	11	46	57
Total	115	152	267

plained by the prevailing policy of early institution of active hemostasis. After manual removal of retained placentas from twenty-seven primiparas and thirty-one multiparas, hemorrhage occurred for which intrauterine packing was required. Undue relaxation or atony of the uterine musculature often is the cause of postpartum hemorrhage and placental retention. Because this relaxed condition of the uterus may persist after manual removal of the placenta, we believe that in these cases uterine tamponade is a valuable prophylactic measure in the event that firm contraction is not induced promptly by other methods. Intrauterine tamponade was employed for twenty-one primiparas and twenty-five multiparas after manual removal of the placenta although no significant hemorrhage had appeared. Intrauterine packing also was carried out, because of persistent uterine atony after cessation of bleeding, for eleven primiparas and forty-six multiparas. The employment of packing in these cases may be called "prophylactic" or "elective." In each case the postpartum hemorrhage seemed to be controlled, but the uterus remained in an atonic condition, and as a precautionary measure the pack was inserted, before the patient was returned to her bed.

One hundred seventy-five of the 267 patients (sixty-three primiparas and 112 multiparas) had relatively easy deliveries consisting of 139 spontaneous and thirty-six outlet forceps deliveries. The remaining ninety-two patients (fifty-two primiparas and forty multiparas) were delivered by more formidable procedures than outlet forceps. The various deliveries and their number are shown in Table II.

Interesting obstetric abnormalities present in this group of 276 patients are listed in Table III. These abnormalities were chiefly defects of the placenta or placental site, which, when present are likely to be important factors in the

TABLE II. TYPE OF DELIVERY AMONG 267 WOMEN REQUIRING INTRAUTERINE PACKING

DELIVERY, TYPE	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	41	98	139
Outlet forceps	22	14	36
Forceps unqualified	4	1	5
Low forceps	22	8	30
Mid forceps	3	2	5
High forceps		1	1
Breech deliveries (all types)	7	8	15
Version and extraction	1	7	8
Unspecified	7	7	14
Destructive	2		2
Forceps rotation	2		2
Dührssen's and forceps	2		2
Multiple			
Twins	2	5	7
Triplets		1	1
Total	115	152	267

that we have followed with reasonable uniformity the rule of withholding massage of the uterus until symptoms indicate that placental separation has occurred. When evidence of separation of the placenta is present, and the placenta has not been expelled spontaneously, or if copious bleeding occurs, the placenta is delivered by simple expression. If the placenta is retained without signs of separation for more than twenty minutes, or if bleeding persists, an attempt is made to deliver the placenta by the Credé maneuver. Failure of this attempt calls for a rest of at least five minutes to permit relaxation and perhaps separation of the placenta, after which the Credé maneuver is repeated at intervals of, perhaps, ten minutes, for approximately an hour post partum. Delivery of a retained placenta by the Credé maneuver is facilitated, in some instances, by sufficient anesthetization of the patient to relax the uterus. In case the placenta has not been delivered within an hour, or in case bleeding requires interference before this time has elapsed, the patient is anesthetized and the placenta is delivered manually.

After delivery of the placenta, an atonic uterus or persistent bleeding indicates the need for vigorous massage of the uterine fundus and, usually, for the intramuscular or preferably intravenous administration of an additional oxytocic agent in the form of an active aseptic ergot preparation.

Indications for Intrauterine Packing

If bleeding continues to be excessive in spite of the treatment we have outlined, the uterus is packed firmly with sterile gauze. Packing is most imperative when the uterus exhibits a continuing tendency to relax. Special instruments for packing have been tried and abandoned. The most effective results are obtained when packing is carried out as follows. Two fingers are inserted in the uterus, with the palm of the hand anterior. The gauze is carried along the fingers with a blunt-nose packing forceps or placental forceps or, in some instances, with the first and second fingers of the other hand. Washed iodoform gauze 2 inches (5 cm.) wide in 5 yard (4.6 m.) lengths is employed, and several lengths are tied together when more packing is necessary to fill the uterus completely. In cases of severe bleeding from an atonic uterus, the vagina also is packed tightly. When the delivery has been complicated by placenta previa, uterine and vaginal packs usually are placed as a precautionary measure, even though bleeding is not pronounced.

Uterine tamponade has been employed in certain cases of postpartum hemorrhage on the obstetric service at the Mayo Clinic since 1918. The procedure is carried out without undue delay as a hemostatic measure in cases in which postpartum bleeding is not readily controlled by oxytocic agents and uterine massage. From January 1, 1918, to December 31, 1945, there have been approximately 12,000 deliveries, and in the course of this period uterine tamponade has been done 267 times, an incidence of 2.3 per cent.

The indications for the employment of intrauterine tamponade among these 267 patients are summarized in Table I. The uteruses of fifty-six primiparas and fifty multiparas were packed because of persistent uterine hemorrhage after the third stage of labor; in four of these primiparas and in seven of the multiparas clinical signs of shock had developed. The average amount of blood lost through hemorrhage by the primiparas was 690 c.c. The average amount of blood lost in the same way by the multiparas was 620.7 c.c. The low average amount of blood lost for which tamponade was done is perhaps ex-

after postpartum hemorrhage for which the intrauterine pack was not employed. Hunt reported a series of seventy-seven cases, involving the years 1934 to 1941, in which the intrauterine pack was employed for postpartum hemorrhage; in the last five years of his series the incidence of febrile morbidity was 4.4 per cent among forty-six patients for whom the intrauterine pack was employed.

Apparent causes for the febrile reaction in our series were infection of the breasts, one instance; infection of the urinary tract, ten instances; phlebitis and embolism, two instances; uterine infection, six instances; and undetermined cause, ten instances. If correction is made for those patients who had infection of the breasts or the urinary tract, phlebitis, and embolism, the number of patients who had a febrile postpartum course consequent to packing of the uterus would be sixteen (including those who had febrile reactions of undetermined cause), an incidence of 6 per cent.

Fatality Rate

There was one death. The patient was a para viii, gravida ix, 39 years old, in whom rupture of the amniotic sac occurred forty-eight hours prior to the onset of labor. After several vaginal examinations carried out in the home, the patient was brought to the hospital. She was delivered of triplets after prolonged first and second stages of labor associated with poor uterine contractions. The placenta was retained; after seventy-nine minutes moderate hemorrhage developed. When efforts to deliver the placenta by the Credé maneuver failed, the placenta was removed manually and the uterus was packed. There was postpartum febrile morbidity, and hemolytic streptococci were found in the uterus. The patient died on the eighth day post partum (this death occurred prior to the advent of the chemotherapeutic agents). Incidentally, no death from hemorrhage occurred in the ten years prior to the time of this report in more than 7,000 deliveries.

Summary and Conclusions

Since 1918, we have employed the intrauterine iodoform pack as a hemostatic agent in certain instances of persistent postpartum hemorrhage. This method of hemostasis has given excellent results when it has been carried out aseptically before the loss of blood became severe.

The chief indications for uterine tamponade are persistent postpartum hemorrhage from an atonic uterus or from the placental site, shock, and manual removal of the placenta.

The morbidity rate of the series of patients for whom uterine tamponade was done was not unduly high (10.9 per cent). In comparison, the morbidity rate among patients who were anemic as a result of postpartum hemorrhage and whose uteruses were not packed was 13.1 per cent. The one death in the series presents convincing evidence of the danger of carrying out obstetric procedures through a contaminated birth canal. Perhaps, if such a patient were admitted to the obstetric service today, the use of penicillin or chemotherapy might alter the outcome.

One of us (R.D.M.) has employed the intrauterine iodoform pack for more than thirty years. In that period, only one patient has exhibited sensitivity to iodine. The reaction consisted of slight generalized erythema which appeared after two successive deliveries in which an intrauterine pack of iodoform gauze had been employed. The first episode was thought to be a reaction to barbit-

causation of postpartum hemorrhage. There appears to have been a tendency for these abnormalities to occur in multiparas, for in eighteen cases of such abnormalities, fifteen patients were multiparas and only three were primiparas. Three patients had uterine fibromyomas.

TABLE III. ABNORMALITY OF PLACENTA AMONG WOMEN REQUIRING INTRAUTERINE PACKING

	PRIMIPARAS	MULTIPARAS
Partial placenta previa		6
Central placenta previa		2
Complete separation of placenta		1
Premature separation of placenta	1	
Abruptio placenta	2	2
Circumvallate placenta		1
Bilobed placenta		1
Succenturiate lobe of placenta		2
Total	3	15

Persistent Bleeding Despite Intrauterine Packing

Persistent postpartum bleeding ordinarily is controlled by a well-placed intrauterine pack. Six of our patients, three primiparas and three multiparas, continued to bleed through the pack. The bleeding of three of these six patients was controlled effectively by repacking of the uterus. However, the hemorrhage of the remaining three patients could not be controlled by the use of oxytocic agents, massage, or the reinsertion of an intrauterine pack. Hence, abdominal hysterectomy was done.

The first of these three latter patients was a primigravida 31 years old. A uterine fibromyoma was discovered during her prenatal examination. Delivery was spontaneous, after an uneventful pregnancy and labor. Because of repeated postpartum hemorrhages not controlled by any of the usual measures or by snugly placed uterine tampons, subtotal hysterectomy was performed.

The second patient, 37 years old, para iii, gravida iv, had bleeding from a marginal placenta previa. Artificial rupture of the amniotic sac controlled the hemorrhage from the placenta previa, and a normal infant was delivered. Postpartum hemorrhage, however, was uncontrolled, and total abdominal hysterectomy was done.

The third patient, para viii, gravida ix, 36 years old, was delivered spontaneously after unusually rapid first and second stages of labor. The placenta was removed manually because of immediate profuse postpartum hemorrhage. Bleeding continued from an atonic uterus which was firmly packed; 1,000 c.c. of blood was transfused to the patient. The packing was removed after twelve hours; a state of mild shock ensued. The appearance of signs of peritoneal irritation and persistent low blood pressure led to a diagnosis of ruptured uterus, which was confirmed at the time of abdominal hysterectomy. Rupture of the uterus may have been caused when the placenta was removed, or by either the violence of the uterine contractions during the precipitate labor, or by packing of the uterus.

Febrile Morbidity Rates

The morbidity rate among patients whose uteruses have been packed is not high. If the accepted standard for febrile morbidity of 100.4° F. (38° C.) persisting for two successive days exclusive of the first postpartum day is employed, then twenty-nine of the 267 patients are included in the morbidity group. This produces an uncorrected morbidity rate of 10.9 per cent which is lower than the morbidity rate (13.1 per cent) among patients with anemia

her nursing her baby, and robs her of a high level of health and happiness which she deserves, and burdens her with several months of invalidism.

During the last ten years we have been advising that a simple sterile uterine packing unit be placed in every delivery room, so that, when a postpartum hemorrhage occurs that cannot be controlled by the well-known methods suggested by Dr. Mussey, it can be stopped immediately and without delay by properly packing the uterus. This will almost invariably arrest the bleeding. We believe that in the smaller hospitals at least, it is better and easier to prevent blood loss than to replace blood loss when it cannot be done immediately. Dr. Mussey states that in the Mayo Clinic the incidence of uterine packing is once in about 430 times. We know of other hospitals where it occurs once in 150 times. Dr. Davis informs us that in the Chicago Lying-in Hospital where the routine administration of ergotrate intravenously is done while the child is being born, the incidence of uterine packing has almost reached a vanishing point.

Concerning the various chemicals and antibiotics that have been and are being used in the pack, we wish to state that through the courtesy of Johnson and Johnson Research Department, because of our interest in uterine tamponade, we have been presented with six dozen packages of gauze impregnated with crystalline potassium penicillin, chemically sterilized and hermetically sealed in glass containers. This pack will remain sterile for an indefinite period, which is important. We are placing these packs in a few hospitals in our State for experimental study.

We believe that further progress will be made toward improving the efficiency and safety of the uterine pack.

Absorbable oxidized gauze is being used to control hemorrhage in general surgery and this or some other preparation may become of practical value in controlling postpartum hemorrhage.

In conclusion, we suggest (1) greater care must be exerted to control postpartum hemorrhage; (2) uterine tamponade carefully and efficiently performed without delay is often a lifesaving measure; (3) it is better in some environments to prevent loss of blood by packing the uterus, than to attempt to replace blood loss where blood transfusion is not immediately available. Further research work is necessary to increase the efficiency and safety of this procedure. We look forward to the time when hemorrhage, and especially postpartum hemorrhage, will play a much more minor role in maternal mortality than it does today, but for the present we submit that while a uterine pack should rarely be necessary, it should always be available, in the delivery room of every hospital.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I would interpolate here that the situation detailed by Dr. Campbell is quite foreign to the consideration of this matter as it pertains to great clinics like Dr. Mussey's and others which are well organized to combat hemorrhage. And I would not at all quarrel with what he pointed out, in what I am about to say now.

The essayists have pointed out a lag in the improvement of statistics in puerperal deaths from hemorrhage, implying perhaps that further improvement in that regard might be attained by a wider appreciation, and a more frequent use, of a number of measures, among them that of the intrauterine pack. While our own management of the third stage of labor currently differs in detail from that sketched in the paper, I would entirely concur with the author in the great importance of that management in the prophylaxis of postpartum hemorrhage. Indeed, I would almost feel that the conduct of that stage constitutes the primary responsibility of the obstetrician, and that he had better delegate the actual delivery of the baby to a subordinate, rather than this responsibility.

In the management of the hemorrhage itself, the authors esteem the intrauterine pack as a prominent and valuable hemostatic measure, so much so that they actually employ it rather extensively in prophylaxis against potential bleeding. But they do admit that in some cases it has failed to control bleeding. In our clinics we would exactly reverse this emphasis. We believe that it fails to control bleeding not responding to other measures and is unnecessary in those cases which do.

urates, but, after the rash had appeared for a second time, it was attributed to sensitivity to iodine.

Available evidence indicates that the employment of the intrauterine pack to assist in control of persistent postpartum hemorrhage has a definite place in the management of this condition.

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Discussion

DR. ALEXANDER M. CAMPBELL, Grand Rapids, Mich.—There are a number of arguments against uterine tamponade in the management of postpartum hemorrhage, some of which are as follows: (1) that it is a nonphysiologic procedure; (2) that it is rarely, if ever, necessary if labor is properly managed, particularly in the third stage; (3) that there is too much danger of infection; (4) that it will not always stop the hemorrhage; (5) that one may pack a uterus that has been ruptured and that packing may actually produce a rupture.

If hemorrhage could always be prevented when it occurs during maternity, obstetrics would soon become a most popular and provocative specialty. The fear of fatal bleeding hangs over the accoucheur's head like the "sword of Damocles," for he never knows when it will occur nor how small an amount of blood will be disastrous.

We believe that more pregnant women die from hemorrhage than from any other cause and, as Dr. Massey has stated, the majority of such deaths are due to postpartum hemorrhage. Of the three great messengers of death in maternity, hemorrhage plays the most important and dramatic role.

We would like to believe that it is never necessary to pack a uterus, but until the standard of care of the parturient woman is considerably improved, this consummation will probably never be achieved.

In my official capacity as maternal health consultant in the State of Michigan, we are chiefly concerned with maternal care as it is conducted in rural areas and in small hospitals where it is impossible to immediately replace dangerous blood loss. We are seriously concerned when a woman bleeds to death from postpartum hemorrhage, but we submit that frequently there is not sufficient concern over the woman who does not die but who sustains mass hemorrhage which invites infection, delays her convalescence, interferes with

The author has described his method of the management of the third stage of labor and while methods of management vary in some respects, the fundamentals remain the same in all clinics—whether oxytocics should be given during the expulsion of the child immediately following or only after the placenta has separated and been expelled is mostly a matter of individual experience. There are, however, many instances of retained placenta following the use of pituitary extract administered before the separation of the placenta has occurred. We have tried all methods and at the present time are administering an oxytocic after the placenta has been expressed, the oxytocic used being ergometrine intravenously or intramuscularly. The only exception to this rule of awaiting placental separation is in the presence of excessive bleeding, when our method of management is similar to the author's, i.e., attempts are made to separate and express the placenta by means of a Credé maneuver. If this fails and bleeding persists, manual removal is done, associated with or followed by the administration of intravenous ergometrine, plasma, and blood, and the uterus is immediately packed. With respect to packing of the uterus, it seems to me that arguments against it are not valid. The fear of infection is exaggerated and has in the past been overemphasized. It is not the entrance of a pack into the uterus that is the factor behind infection, but rather the loss of blood. Neither is the type of pack of too great importance—whether wet or dry, and if wet whether this or that antiseptic is used. What is more important is that when packing is necessary it should be done early, promptly, and thoroughly. The amount of gauze used should be just sufficient to cause the uterus to contract firmly—about 5 yards. To overpack the uterus will defeat the purpose of a pack by distending the uterus and, so partially paralyzing it, resulting in more bleeding.

If an intra-uterine pack fails to control bleeding it is nearly always the result of overdistention of the uterus by too large a pack, except in cases of neoplasm, or placenta accreta. It is therefore wiser to "underpack" rather than "overpack" the uterus.

In most instances when packing is necessary it is also wise to pack the vagina. With the discovery of "Oxyel," we may have an agent of great value for the control of hemorrhage, but at present the strips of material are too small to be efficiently useable in an emergency. I have been given to understand that Oxyel in strips of 1 yard long and 2 inches wide will soon be obtainable.

Between the years of 1940 and 1946 on the old standard of determining postpartum hemorrhage, we had approximately 112 cases, but under the new classification of 500 c.c. or more and with the hemoglobin dropping below 70 per cent, there were 674 cases.

In spite of this apparent increase in postpartum hemorrhage, the mortality is considerably less because of the use of plasma, blood, and prompt intrauterine packing. In fact, during this latter period there was one death in 338 cases of postpartum hemorrhage. This death could have been avoided if the gravity of the patient's condition had been recognized and the uterus promptly packed; because she rallied for a time from her severe blood loss, but the subsequent so-called slight bleeding was sufficient to result in death, in spite of 3,500 c.c. of plasma and blood.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—I am not sure it is wise to prolong this discussion indefinitely as to opinions in regard to the use of the intrauterine pack, but I cannot refrain from saying a word for it, particularly in its relationship to teaching young students and medical practitioners. I feel that there is certainly ample ground for us to cling to that teaching of this subject. Naturally, a pack in the uterus in its attached position interferes with the contractility of the organ. And yet it is a stimulus, or so it seems to us, to uterine contraction. Again I think it is important in the postdelivery phase of placenta previa. We lose our cases with hemorrhage after delivery as well as before delivery unless we prevent hemorrhage, take careful provisions to do so by pack or by insurance that there is no bleeding from the lower uterine segment where it is likely to occur. Unless this is done there will be continued deaths from so-called antepartum hemorrhage which causes death in the postpartum period.

Again, I doubt if oxytocic agents are safe for the instruction of medical students and interns. Even trained obstetricians have delivered the first fetus and found that there

They say that uterine packing was used 267 times in their hands in 11,651 deliveries, an incidence of 2.3 per cent. Had the same ratio been applied to the 8,400 cases delivered by us in 1946 alone, we would have used it 193 times. We did not, in fact, use it in a single case, but we lost no cases in that time from postpartum hemorrhage. Our failure to use the intrauterine pack, therefore, cannot be assigned as a cause of increased mortality from postpartum hemorrhage.

Moreover, in reviewing such deaths, both in our own earlier experience, and from published reports from other clinics, as well as from information gained by personal observation and communications from other sources, a majority of the fatalities due to postpartum hemorrhage *were* subjected to packing. This would seem to indicate the futility of the packing in at least the worst cases of inertia. Besides its futility, its use has been time consuming when time is precious, has sometimes concealed significant continuing hemorrhage, and has more than possibly concealed more or less obscure pathology causing bleeding, which has been mistakenly attributed to inertia. This would actually appear to have been possible in the essayist's third case of hysterectomy.

The essayists' use of tamponade in a large series of cases in none of which the average blood loss exceeded 600 c.c., and in 57 of which it was employed after bleeding had ceased, and in 47 of which *bleeding never had occurred at all*, would seem poor evidence of the necessity of this procedure in *any* case, and certainly does not constitute proof that it contributes to the lowering of hemorrhagic mortality.

I, therefore, cannot refrain from reiterating my belief that: uterine tamponade for postpartum hemorrhage is unphysiologic because it directly circumvents the effort otherwise made to empty completely the uterine cavity, reduce that cavity to the smallest size possible and the bulk of the myometrium to the smallest mass possible; that it is unnecessary in the less severe cases and futile in the more severe ones; that it may actually militate against the patient by loss of time in resorting to more definitive surgical measures; by obscuring accurate diagnosis; and by hiding continuing significant hemorrhage.

DR. GERALD C. MELHADO, Montreal, Canada.—The frequency and severity of postpartum hemorrhage bears a definite relation to the management of the third stage of labor. That this incidence shows no appreciable decrease, but is in fact increasing, may be verified by a careful analysis of records in almost any clinic.

One reason for this increase is undoubtedly due to more rigid criteria as to what constitutes hemorrhage. Some years ago most clinics were satisfied to estimate the blood lost, but in recent years the measured amount of blood and the hemoglobin determination are the deciding factors.

In our clinic at the Royal Victoria Maternity Hospital a blood loss of 500 c.c. or more and a hemoglobin below 70% is classified as a postpartum hemorrhage. Severe blood loss does not always seriously jeopardize the patient's life while, on the other hand, a loss of less than 800 c.c. has resulted in death.

A factor of no small importance, therefore, is directly related to the proper prenatal care of anemic states. It is also well to remember that blood loss bears some relation to size of the baby, placenta, and is influenced by anesthesia and the duration of labor.

Knowledge of the mechanism of placental separation must be kept in mind if undue hemorrhage is to be avoided, whether one accepts the older idea of separation by means of a retroplacental hematoma, or the more modern view of a decrease in size of the uterine cavity and area of placental attachment leading to a partial and finally complete separation. In the modern view as the uterus contracts and retracts its walls become thicker and thicker and the area of placental attachment smaller, so that eventually the compact placental can no longer follow the changes and is consequently separated from the uterine wall.

We are, therefore, of the opinion that no attempt should be made to hasten this process by massage of the uterus, or to endeavor to express the placenta before separation has occurred; for this endeavor to hasten placental separation is a basic factor in many instances of postpartum hemorrhage.

The reason we have so few cases of hemorrhage, I think, is that we are very conservative. First of all, we teach the students and residents that the placenta will not be pushed out before half an hour after the birth of the child.

Second, regarding the anesthesia, in Holland we very rarely use an anesthetic in a normal delivery. Of course, it is always used in an artificial delivery, in my clinic most times spinal anesthesia. In those cases where it is necessary to have relaxation of the uterus, e.g., in version and extraction, general anesthesia is given. I think if we are fairly conservative in the choice of our anesthesia and think of the possibility of its influence on the uterus, that then the chance of bleeding will be much less. In cesarean section we never pack, and in placenta previa only in a very few cases where it is not possible to stop the bleeding.

DR. ARTHUR H. BILL, Cleveland, Ohio.—If one encounters a well-developed postpartum hemorrhage he will realize that the surest treatment of this condition is prophylaxis. I believe in starting immediately with the birth of the child to stimulate the uterus to contract and prevent loss of blood in the third stage. If the uterus fills up with blood before the placenta is delivered, a considerable loss of blood may be encountered. Shortly after the introduction of pituitrin I inaugurated a plan of giving pituitrin immediately upon the birth of the child, and then giving an ergot preparation immediately upon the separation of the placenta. We have used this procedure for more than thirty years in every case. That means that we have used an oxytocic in about 100,000 cases, and I have not encountered a case of retention which could be attributed to pituitrin. I have however, been reluctant to give ergot until the placenta is ready to be delivered. I prefer pituitrin first, and intravenous ergotrate as soon as the placenta is separated. In my practice I have been through all the various stages from hot douches to the present-day methods, and in the early days of my practice I packed with iodoform gauze very frequently. We had no oxytocics, no pituitrin, no reliable ergot preparation, and no blood transfusion, and did not know what the blood pressure was, for we had no sphygmomanometer. We would pack the uterus with little hesitation, but this was not always successful. Often after packing the fundus was hard and everything seemed satisfactory. A few minutes later the uterus would soften and fill with blood behind the packing. A relaxed uterus cannot really be packed. Again, too much packing keeps the uterus unnaturally distended. Since the routine use of oxytocics we pack less and less. In fact, packing for postpartum hemorrhage is seldom used. Personally I cannot recall having done so for a number of years.

Why is it that the mortality in postpartum hemorrhage is still as high as stated? In our experience one of the most satisfactory things in the progress of obstetrics has been the reduction of postpartum hemorrhage. We see it very rarely. In addition to the routine administration of a pituitary preparation, a hand should be kept on the fundus continuously during the third stage and if relaxation occurs the oxytocics should be repeated. Try to keep the uterus from filling up with blood before the placenta is expelled, for loss of blood predisposes to more loss of blood by causing uterine relaxation. In my opinion, routine use of oxytocics has greatly reduced the necessity for packing. I agree with what Dr. Cosgrove has said.

DR. MUSSEY. (Closing.)—I am aware of the vast experience of Drs. Cosgrove, Baer, and Bill, and appreciate their constructive criticism. I agree with Dr. Bill, as we have mentioned in the paper, that prophylaxis is of primary importance in this condition and that management of the third stage should be conducted with a minimum of manipulation of the uterus.

However, my colleagues and I feel that the use of the intrauterine pack has a place in the management of postpartum hemorrhage. This position is upheld by a majority of writers on this subject and has been approved by Dr. Campbell, Dr. Montgomery, and others today. Our distinguished friend from Holland states that in his country little or no analgesia and anesthesia are employed in labor. I agree with him that the use of these agents seems

was a second fetus contained in the uterine body. If we teach the use of oxytocics we run the danger that our students and interns may overlook that possibility and have trouble.

Again, in the cases where there is difficulty in the delivery of the aftercoming shoulder and the baby's body, I think danger is incurred with the administration of ergot immediately after the birth of the head. One of my men has been trying this and encouraging me to employ it, but I think that in the third stage oxytocic agents should not be used.

Personally, we use the intrauterine pack very frequently. I think our results have been increasingly better with cases of postpartum hemorrhage, but of course the best improvements have come with the blood bank and the plasma. In the large hospital practice I think this is due to the great availability of the intravenous fluids and blood.

DR. JOSEPH L. BAER, Chicago, Ill.—I think it best to limit my remarks to the experience that we have had at the Michael Reese Hospital where we went through the phases of the hot douche, the one-hour holding of the fundus uteri after delivery and the frequent use of the pack to the more recent techniques. We adopted the ergotrate intravenous procedure as soon as it was proposed. We use it immediately upon the stemming of the shoulder under the symphysis. We have yet to encounter the theoretical risk of locking a second fetus. The frequency of the use of the pack has dwindled with us almost to the vanishing point. I am in complete accord with Dr. Cosgrove's analysis on that position: that, used when there is little hemorrhage it is superfluous; used when there is a pathologic condition, when the uterus is prevented from controlling its own bleeding, it is futile.

The experience of the accoucheur plays a very important role in the interpretation of what constitutes postpartum hemorrhage. If a man has had an unhappy experience with perhaps a fatal hemorrhage, he is quite prone to look upon the next instance of bleeding with a considerable degree of anxiety and resort to immediate and vigorous measures of control which may be entirely superfluous. Furthermore, I think employment of the pack is in reverse proportion to the experience of the accoucheur.

I agree again with Dr. Cosgrove who believes that the resident may well be left to the delivery itself, and the third stage supervised by someone more experienced than he.

I think it might be of interest to this group to know that the problem confronting Dr. Campbell in the State of Michigan, which is a problem also confronting the small institutions all over the United States, is by way of being solved to some extent in the next several years, namely by the availability of blood. The National Red Cross is preparing to develop a nationwide service in the obtaining and distributing of blood for all indications in which blood transfusion is required and, of course, in that group the maternity patient comes almost first. The American Medical Association has given its approval to this endeavor of the National Red Cross, provided it is carried out on a community level and with the cooperation and consent of the local county medical societies. I am inclined to think that this will in due course make blood available in adequate quantities for many smaller institutions which do not now have this remedy. From the standpoint of the patient in the third stage of labor it is far better to give her a replacement of 500 c.c. than to resort unnecessarily to the intrauterine pack.

DR. VAN ROUWDIJK BASTIAANSE, Amsterdam, Holland.—Regarding hemorrhage in the third stage of labor, in our clinic we rarely observe severe bleeding post partum. I doubt if there has been one patient in our 9,000 deliveries who has been packed in the years 1923 to 1938 in the obstetric department of which I was head before I was appointed head of the department of obstetrics and gynecology of the University of Amsterdam. Of our hospital patients, who had prenatal care, including those patients who had cesarean section for placenta previa, etc., the mortality was less than one in a thousand. In our clinic in Amsterdam we also have very seldom seen bleeding—I cannot give you the figures, but I am sure that we have not used the intrauterine pack more than once a year in about 2,300 deliveries a year.

MATERNAL CONGENITAL HEART DISEASE AS AN OBSTETRIC PROBLEM*

CURTIS J. LUND, M.S., M.D., NEW ORLEANS, LA.

(From the Department of Obstetrics and Gynecology, University of Minnesota Medical School)

HEART disease is displacing infection, hemorrhage and toxemia as leading causes of maternal mortality.¹ The death rate from heart disease in pregnancy is declining too but at a slower rate. Since rheumatic heart disease is by far the most common cardiac disease in pregnancy, it has received the most attention.

Congenital heart disease is uncommon in pregnancy but it is by no means as rare as the older literature suggests. In 1938, Jensen² reviewed the literature and recorded 115 cases. Almost all were in the form of single case reports. However, since that time, Hamilton and Thomson³ described twenty-eight more. Other authors^{1, 4} have reported a score or more. These numbers forecast an increasing frequency of this complication. The increase is likely more apparent than real because of better skill in recognizing these lesions.

For the present at least, management of rheumatic heart disease in pregnancy is more or less satisfactorily standardized. Now other forms of heart disease require similar study. Do pregnant women with congenital heart disease present a problem similar to those with rheumatic disease? If not, what are the differences? It is the purpose of this paper to show that differences do exist not only between the various types of heart disease but also within the group of congenital lesions.

Observations

During the past ten years, twenty-five women have been admitted to the University Hospitals of the University of Minnesota Medical School because of pregnancy complicated by congenital heart disease. These mothers were delivered of twenty-nine babies in this clinic. Several had been delivered elsewhere earlier so that a total of forty-five deliveries was recorded for the group.

Age and Parity.—As might be expected with congenital heart disease, the patients were comparatively young (Table I).

TABLE I. AGE AND PARITY

PARITY	AGE IN YEARS				TOTAL
	BELOW 20	20-24	25-29	30-34	
Primiparas	1	8	5	1	15
Multiparas	2	5	5	2	14
Total	3	13	10	3	29

Complications of Pregnancy.—As a group, these were not unusual (Table II). The ominous complications of anemia and infection were common.

Toxemia of pregnancy was a frequent and serious complication. There were eight patients with hypertension but only five had other confirmatory evi-

*Presented by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

to increase the incidence of postpartum hemorrhage. If expectant mothers were fully aware of the risk of their employment in labor there would be less demand for their use.

I may repeat that we have given pituitrin intramuscularly for many years as the baby is being delivered, and in the last ten years we have usually given an aseptic ergot preparation intravenously after the third stage is completed.

We have employed the intrauterine iodoform gauze pack in some cases in which bleeding appeared to be under control, but in which the uterus remained atonic. Many of our staff use the pack more often than is urgently necessary, but they have learned that the early application in the uterus of a washed iodoform gauze pack in cases of uncontrolled or poorly controlled postpartum bleeding, and in the presence of an atonic uterus is much safer than to delay and permit the patient to slip into a condition of shock. Also, we believe that blood transfusions should be used to prevent shock as well as to treat it.

I failed to mention that the pack usually is removed on the morning following its insertion, so that usually it remains in place from, perhaps, four to thirty hours. An iodoform gauze pack which is removed from the uterus, as described, does not have a foul odor. When the occasion arises we employ the intrauterine iodoform gauze pack with caution but without dread.

TABLE IV. DELIVERY AND ANESTHESIA

DELIVERY	TOTAL DELIVERIES	NONE	TYPE OF ANESTHESIA		
			LOCAL	LOCAL + GAS	OTHERS
Spontaneous	19	5	2	9	3
Low forceps	8	0	2	5	1
Cesarean section	2	0	2	0	0
Total	29	5	6	14	4

Anesthesia (Table IV) was usually local with some gas analgesia with uterine contractions.

Maternal Mortality.—There was one maternal death in the series. A case summary appears later in this paper. Another died six months post partum of subacute bacterial endocarditis. This had developed early in pregnancy as a complication of a patent ductus arteriosus.

The Infant.—There were many premature infants: eight in twenty-nine deliveries, or an incidence of 27.5 per cent. Exclusive of the two delivered by cesarean section, the premature labor began spontaneously, frequently while the mother was hospitalized for care during the last trimester. No significant exciting cause could be determined.

Table V shows the distribution of infants according to weight and mortality. Those who did not survive were a set of stillborn macerated premature twins and one full-term infant. The unique circumstances of the only neonatal death warrant a short case summary.

TABLE V. INFANT WEIGHT AND MORTALITY

	1,500* TO 1,999 GM.	2,000 TO 2,499 GM.	2,500 TO 2,999 GM.	3,000 TO 3,499 GM.	3,500 TO 3,999 GM.	4,000 GM. AND OVER	TOTAL
Total live births	2	6	2	10	4	4	28
Neonatal deaths	0	0	0	0	0	1†	1
Survival	2	6	2	10	4	3	27

*There was one set of stillborn twins weighing 1490 and 1545 grams respectively.

†See text for details.

The mother was a secundipara, 26 years of age. She had known of her congenital heart disease for fifteen years. Her lesion was a ventricular septal defect, Class 2. There had been no change in her cardiac condition during pregnancy. She was referred to the University Hospitals, not because of her cardiac condition, but because she had had a very difficult labor with her first pregnancy. After two weeks of observation it was felt that the baby was becoming excessive in size so labor was induced. Following a one and one-half hour labor, she was delivered spontaneously of a 4,100 Gm. infant, who breathed immediately. The baby soon became cyanotic and died on the following day. Postmortem examination revealed a large ventricular septal defect! The mother has since had a normal infant, and she is living and well five years after her last pregnancy. A somewhat similar case has been reported by Tucker and Kinney.⁵

The remainder of our observations deal primarily with the effect of pregnancy on the congenital heart disease.

Etiology.—The relationship of such factors as heredity, maternal rubella in early pregnancy, and maternal dietary deficiency to the production of congenital heart lesions places the problem of etiology in the sphere of the obstetrician. It is not the purpose of this paper to discuss etiology, but attention is called to two facts: There was the mother with a ventricular septal defect who produced an infant with the same lesion, and secondly, two of the twenty-five women (8 per cent) had a cleft palate and hare lip associated with a patent ductus arteriosus.

TABLE II. COMPLICATIONS OF PREGNANCY

Anemia (hemoglobin below 10 Gm.)	6
Toxemia	5
Cleft palate	2
Pyelitis	2
Respiratory infection	1
Schizophrenia	1
Multiple pregnancy	1
Diabetes	1
Total	19

dence of toxemia. Mild pre-eclampsia, present in three cases, was not a serious problem. Severe pre-eclampsia was associated with congestive failure in its two appearances and was indirectly associated with the only maternal death.

Abortion.—None was observed. There were no therapeutic abortions.

Labor.—Spontaneous premature labor and delivery were common. Exclusive of two cesarean sections done before term, the incidence of premature labor was 22 per cent.

Labor was induced at term twice—once because of an excessive sized fetus in a woman with previous history of dystocia from large babies. The second induction was for severe pre-eclampsia.

Prolonged or difficult labors were not a problem. In fact, the descriptive term, "easy labor" was found on thirteen records. Table III shows the duration of the first and second stages. Three of the patients had precipitate labors and precipitate delivery in bed before they were fully aware of the reality of their labor.

TABLE III. DURATION OF LABOR

HOURS FIRST STAGE	PRIMIPARAS	MULTIPARAS	TOTAL
3	1	4	5
3 6	5	4	9
6 9	4	2	6
9 15	2	1	3
15 21	3	0	3
21 24	1	0	1
Total	16	11	27*
MINUTES SECOND STAGE	PRIMIPARAS	MULTIPARAS	TOTAL
10	3	4	7
10 20	2	4	6
20 30	6	2	8
30 40	3	1	4
40 60	2	0	2
Total	16	11	27*

*Two patients were delivered by cesarean section.

It has been departmental policy to terminate labor by low forceps delivery to reduce the strain of the second stage of labor for all patients with heart disease. Table IV shows that this has been done only occasionally. This discrepancy is best explained by the short duration of the second stage of labor (Table III). There were two cesarean sections, one for acute fulminating pre-eclampsia, and the other to terminate the pregnancy of a patient with congenital heart block who was most difficult to manage medically.

Excessive bleeding post partum was not observed. Seventeen had an estimated blood loss of 200 c.c. or less. None was over 600 c.c.

TABLE VI. TYPES OF LESIONS

Patent ductus arteriosus	13
Intraventricular septal defect	8
Auricular septal defect	4
Pulmonary stenosis	1
Undetermined	3
Total	29

TABLE VII. EVALUATION OF DIAGNOSTIC FINDINGS

MURMUR		ELECTROCARDIOGRAM		X-RAY	
Characteristic	14	Abnormal	8	Characteristic	13
Suggestive	7	Normal	17	Suggestive	9
Questionable	4			Questionable	3
<i>Final Diagnosis</i>					
		Reasonably certain	14		
		Probable	7		
		Possible	4		

a tentative diagnosis of organic heart disease in twenty-three of the twenty-five patients. Only two had the diagnosis made for the first time during pregnancy. In five, the diagnosis was as recent as five years, but the remainder had known of their cardiac condition for many years. Present-day attention to cardiac lesions in infancy and childhood will probably record most of these abnormalities at an early age and long before pregnancy occurs.

Functional Capacity or Cardiac Class.—All patients were catalogued according to the functional classification of the New York Heart Association (Class 1, 2, 3, and 4). Each patient was classified according to her prepregnant state for the purpose of establishing a base line. Then she was reclassified during the first part of pregnancy, the last trimester, labor and delivery, and finally after pregnancy.

Patients were separated according to the type of lesion and the prepregnancy class (Fig. 1). None was in Class 3 or 4 before pregnancy. Twelve of the twenty-nine pregnancies were associated with change in class. The greatest disturbance of class was associated with patent ductus arteriosus where nine of twelve patients exhibited change, and all but one of the Class 2 patients were worse. Only three other changes were noted: two associated with ventricular septal defect, and the other with an undetermined congenital lesion. (One cardiologist thought the latter definitely a ventricular septal defect.)

Even more information can be had by a chronological analysis of those who changed. Fig. 2 shows the amount of change in relation to the duration of pregnancy. Every patient who maintained her prepregnant class through the first part of pregnancy changed no more than one class later in pregnancy. As there were no Class 3 prepregnant patients, this means that no patient of this type failed. On the other hand, every patient who changed in early pregnancy changed one or more classes later. The more serious changes were associated with patent ductus arteriosus.

Fig. 2 also shows the permanent change in class associated with pregnancy. Four mothers never returned to their prepregnancy levels. All had patent ductus arteriosus. Two mothers in Class 1 became Class 2 post partum, and two in Class 2 became Class 4 and ultimately died—one during cesarean section, and the other six months post partum.

Pulse and Respirations.—In 1942, Mendelson and Pardee⁶ claimed prognostic significance to the rate of pulse and respirations of mothers with rheumatic heart disease during the first stage of labor. They believe that the criti-

Diagnosis.—The diagnosis of congenital heart disease most certainly falls outside the sphere of the obstetrician, and inevitably rests upon a competent cardiologist. This study is no exception. The final diagnosis (Table VI) has been based upon the opinions of the cardiologists in the Department of Medicine, and often their final diagnosis was not made until several weeks post partum. We are indebted to these consultants not only for diagnosis, but for invaluable assistance in the management of these patients.

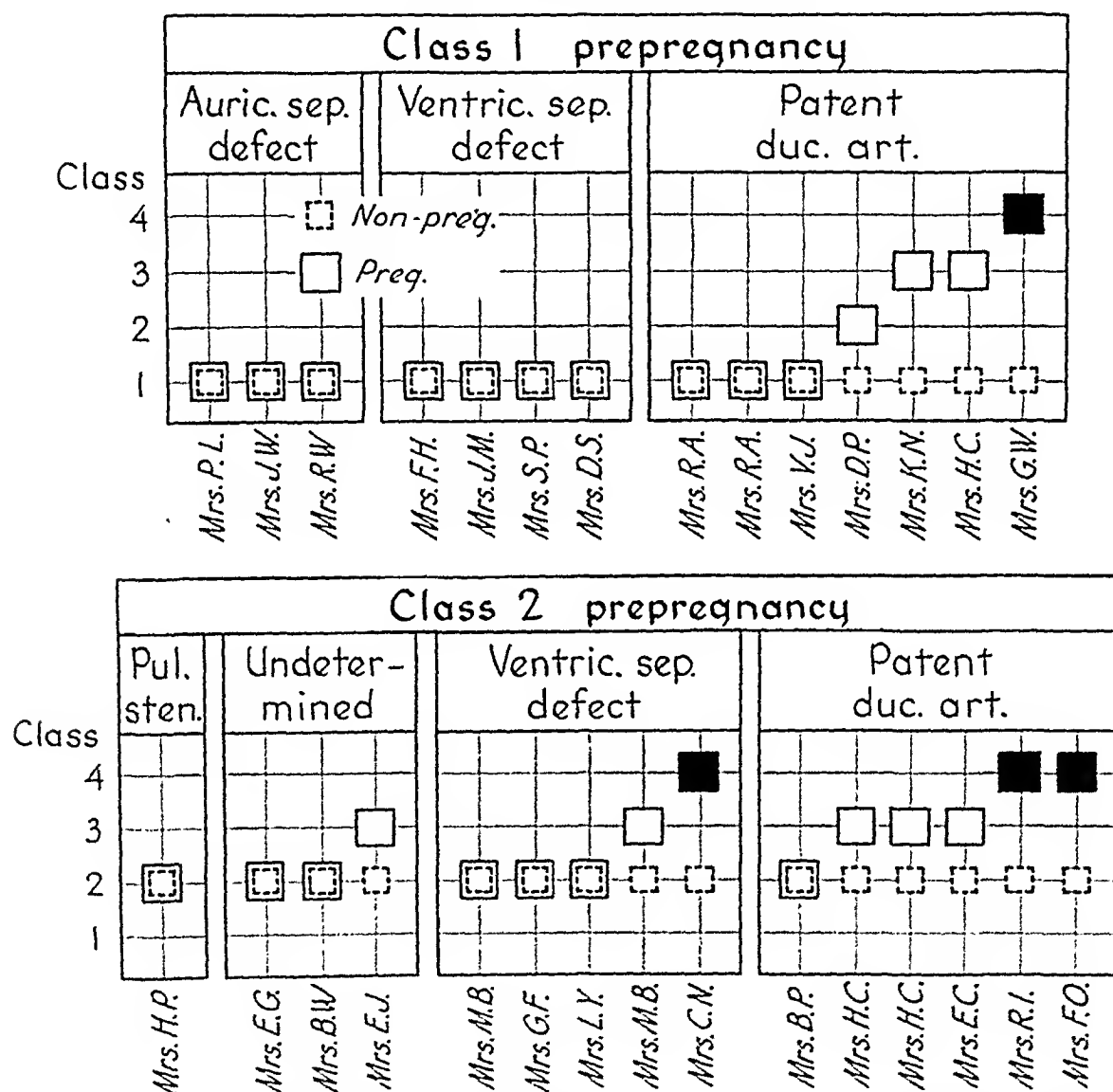


Fig. 1.—Changes in functional capacity in congenital heart disease in pregnancy. Each patient's class (New York Heart Association) before pregnancy and the maximum change produced during pregnancy is listed according to the type of lesion.

Only two points concerning diagnosis seem pertinent to this paper. The first concerns diagnostic accuracy. No patient was included in this study if there was doubt as to the congenital nature of her lesion. However, if comparisons are to be made between the various types of congenital lesions, then detailed diagnosis must be accurate. Table VII shows the relative merits of the common diagnostic criteria and their bearing on the final working diagnosis.

The second point of interest concerns the relationship of the obstetrician to the first diagnosis. Nothing more than a history was necessary to establish

cal levels are 110 and 24 for pulse and respirations, respectively. When rates exceeded these levels, the patient was in imminent danger of heart failure. An attempt was made to review the validity of this rule for congenital disease. Each patient was studied before labor, during labor, delivery, and the puerperium. It must be pointed out that we were unable to obtain readings routinely every fifteen minutes as is suggested. However, the data were quite complete for Class 3 and 4 lesions. Two of the Class 4 patients were always below the critical levels; however, one had a heart block, and the other was digitalized. The other two Class 4 patients had positive findings. There were three Class 3 patients with pulse and respirations above the critical ranges. None failed, but one was dangerously near it. Also, two Class 1 and two Class 2 patients exceeded critical levels without signs of cardiac embarrassment.

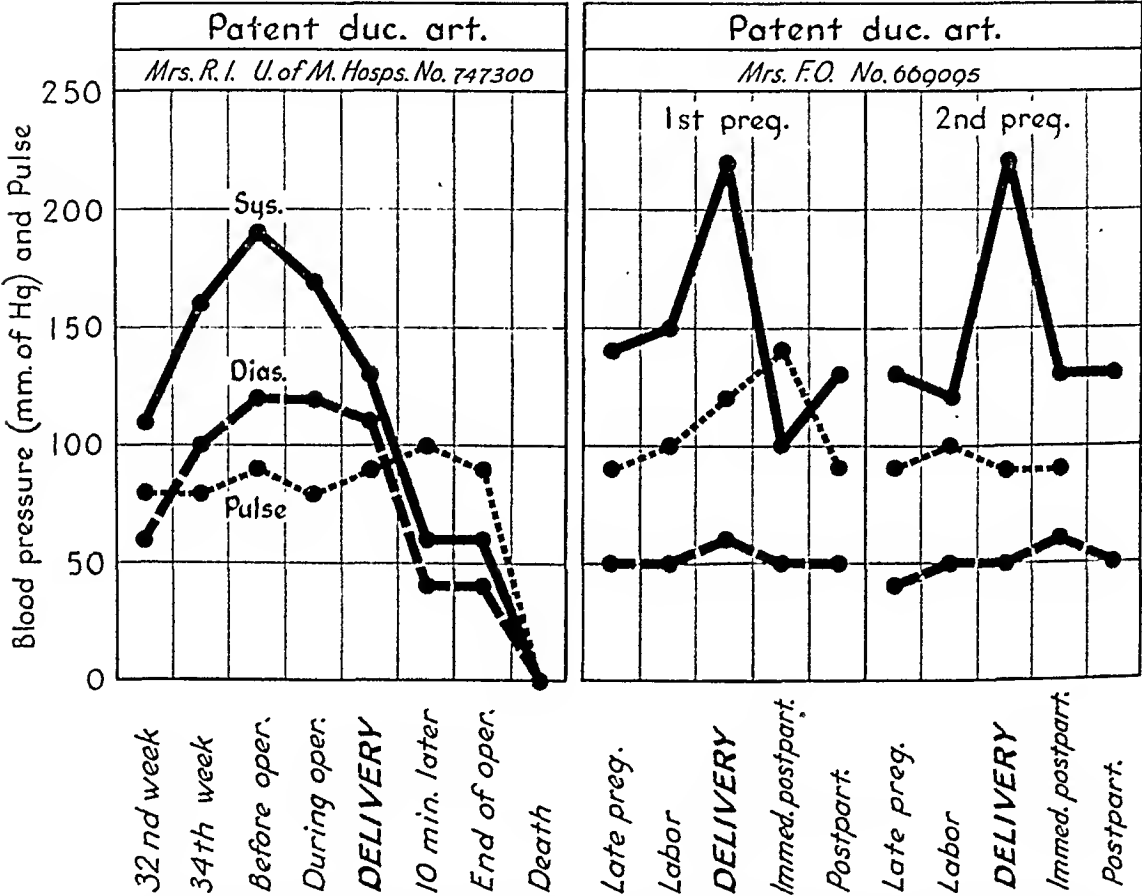


Fig. 3.—Changes in blood pressure during labor and delivery. The shocklike picture which may be associated with delivery is demonstrated. A detailed report of Mrs. R. I. is found in the text. Mrs. F. O. showed similar reactions in two successive pregnancies.

Blood Pressure.—Eight of the patients presented bizarre changes in blood pressure during delivery. In general, the reaction consisted of hypertension followed by a sudden drop in blood pressure to low levels immediately after delivery of the baby.

The hypertension was sometimes present before labor because of toxemia. In others, the hypertension developed spontaneously during labor. In a very few minutes after the baby was delivered—sometimes before and sometimes after the placenta was delivered—the blood pressure dropped dramatically. Three patients lost consciousness. All but one recovered within a few minutes, or at most a few hours. Table VIII lists the details. The labile blood pressure

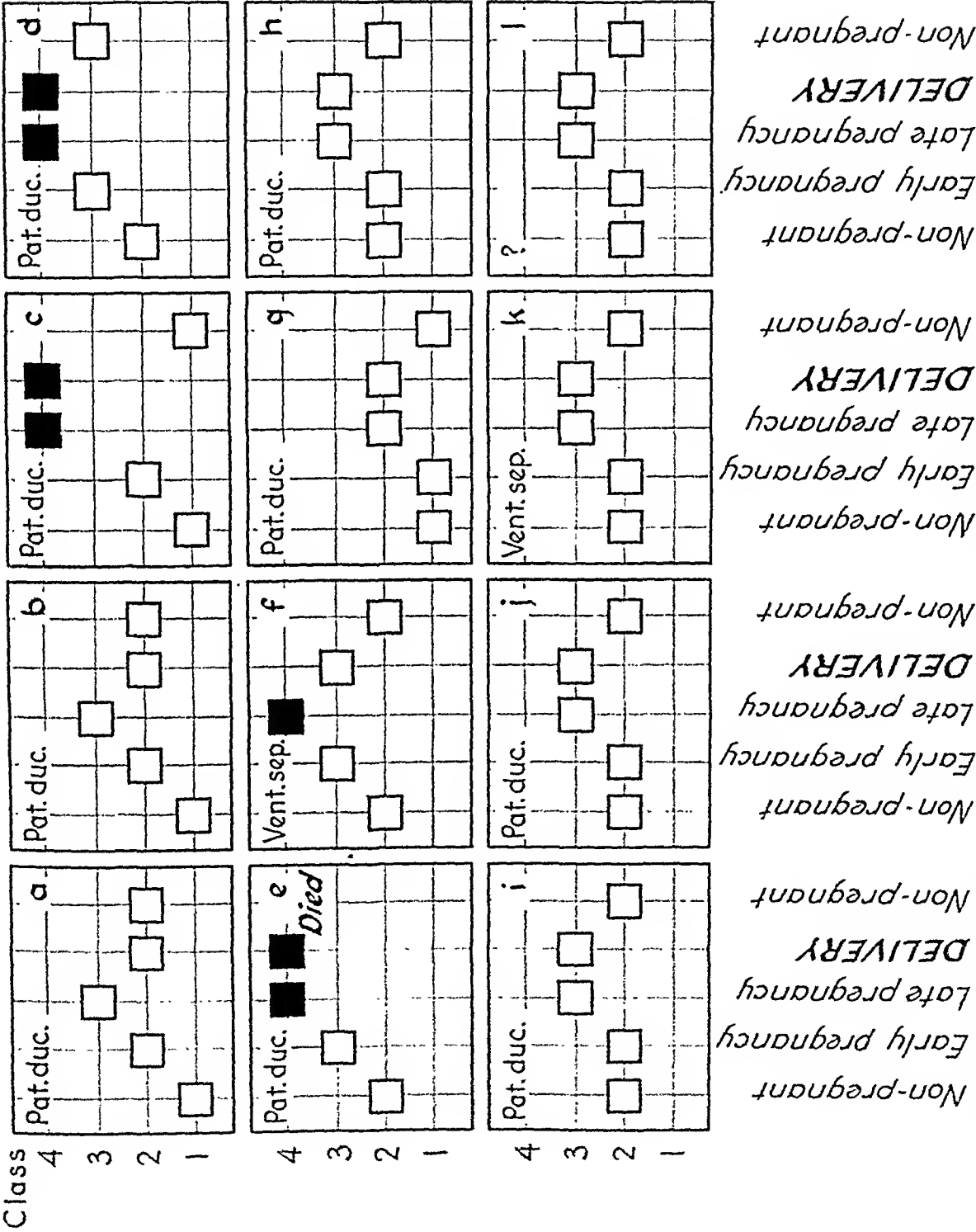


Fig. 2.—Changes in functional capacity in congenital heart disease in pregnancy. This shows the change in class according to duration of pregnancy. Note the unfavorable course of patients a-f whose class changed in early pregnancy.

TABLE VIII. BLOOD PRESSURE DURING LABOR AND DELIVERY

PATIENT	LESION	HIGH-EST CLASS	BLOOD PRESSURE					BLOOD LOSS IN C.C.	OXYTOCIC	LOSS OF CONSCIOUSNESS	REMARKS
			LATE PREG. NANCY	LABOR	DELIVERY	IMMEDIATELY POST PARTUM	PUERPERIUM				
N. C.	Patent Duetus	3	140/50	150/50	220/60	100/50	130/50	100	Pituitrin	0	
N. C.	Patent Duetus	3	130/40	120/50	220/50	130/60	130/50	50	Ergot	0	Repeat performance. See above
E. J.	Patent Duetus	3	130/80	130/70	160/90	95/50	170/70	300	Ergot	Yes	Marked anxiety
F. O.	Patent Duetus	4	120/60	110/60	120/60	90/60	130/60	400	Ergot	0	
R. L.	Patent Duetus	4	160/100	190/120*	130/110†	60/40	----	400	Ergot	Yes	Toxemia. Died. Cesarean section
C. N.	Vent. Septal	4	130/75	150/80*	165/90†	50/35	120/70	300	Ergot	Yes	Cesarean section
E. G.	Undetermined	2	150/80	150/80	160/90	100/60	130/75	150	Ergot	0	Mild toxemia
<i>Hypertension Without Sudden Postpartum Change</i>											
D. S.	Vent. Septal	1	150/105	150/105	160/100	150/105	160/110	200	Ergot	0	Toxemia
D. P.	Patent Duetus	2	115/55	130/60	180/80	170/80	115/60	300	Ergot	0	
G. W.	Patent Duetus	4	180/84	200/80	225/85	190/80	135/65	150	Ergot	0	Toxemia

*Resuming operation.

†After delivery.

was most common with patent ductus arteriosus, but it was seen with septal defects as well. With one exception, the break occurred in patients of Class 3 or 4. Figs. 3 and 4 illustrate individual patients. From Table VIII it is interesting to note that the shock was unrelated to hemorrhage or to pituitrin. One patient exhibited strikingly similar changes in two successive pregnancies (Fig. 3).

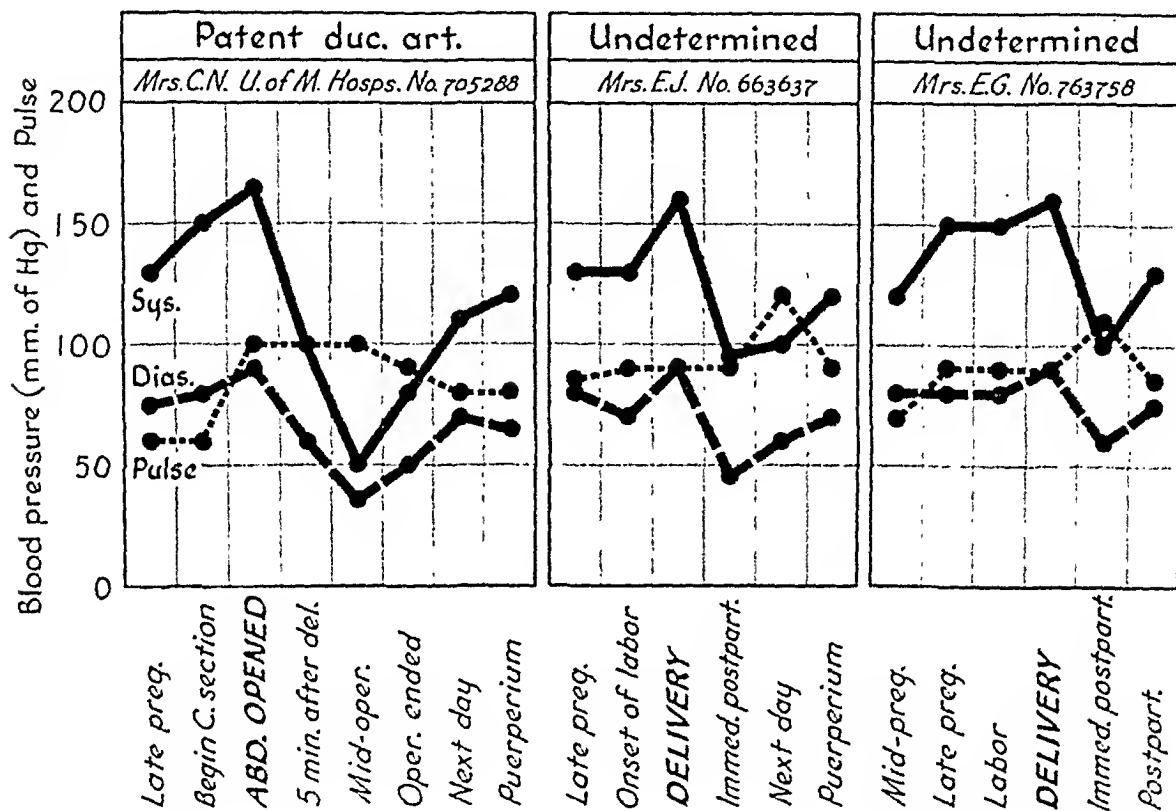


FIG. 4.—Changes in blood pressure during labor and delivery. The hypertension-delivery-shock syndrome similar to Fig. 3.

The following case history describes this picture adequately: A primigravida, aged 26 years, knew she had heart disease as a child. Her only symptom had been dyspnea on moderate exertion. She was first seen at the twenty-fourth week of pregnancy, and a diagnosis of patent ductus arteriosus was made. After complete work-up, she was digitalized, and her activities were markedly restricted. At the thirty-second week, she was progressing nicely without symptoms. Arrangements were made for admission to the hospital for the remainder of the pregnancy, but the patient refused. Two weeks later she suddenly developed edema of feet, hands, and eyelids, dyspnea at rest, orthopnea, and slight cyanosis. Blood pressure, previously 115/60-80, was now 165/100. There was marked albuminuria. She was admitted to the hospital and actively treated for pre-eclampsia. In spite of all therapy, the blood pressure rose rapidly to 200/120, and eclampsia was imminent. The cervix was long, hard, and closed so the only feasible method of delivery was by cesarean section. The operation was done under local anesthesia. Fig. 3 shows the behavior of blood pressure and pulse during operation. The patient remained in shock for about half an hour with a relatively slow pulse and died. Post-mortem examination revealed a patent ductus arteriosus of such magnitude that there was no duct—merely a hole about 1 cm. in diameter between the left branch of the pulmonary artery and the aorta. The right ventricle showed massive hypertrophy being 22 mm. thick, as compared to 14 for the left ven-

tricle. The liver showed the characteristic necrosis of eclampsia. Other findings were not remarkable.

Vital Capacity, Venous Pressure, and Circulation Times.—These tests were made on many patients. They are now done routinely on all patients except those with very minor lesions. While these tests may have some diagnostic value, they are being used primarily as aids in predicting impending failure.

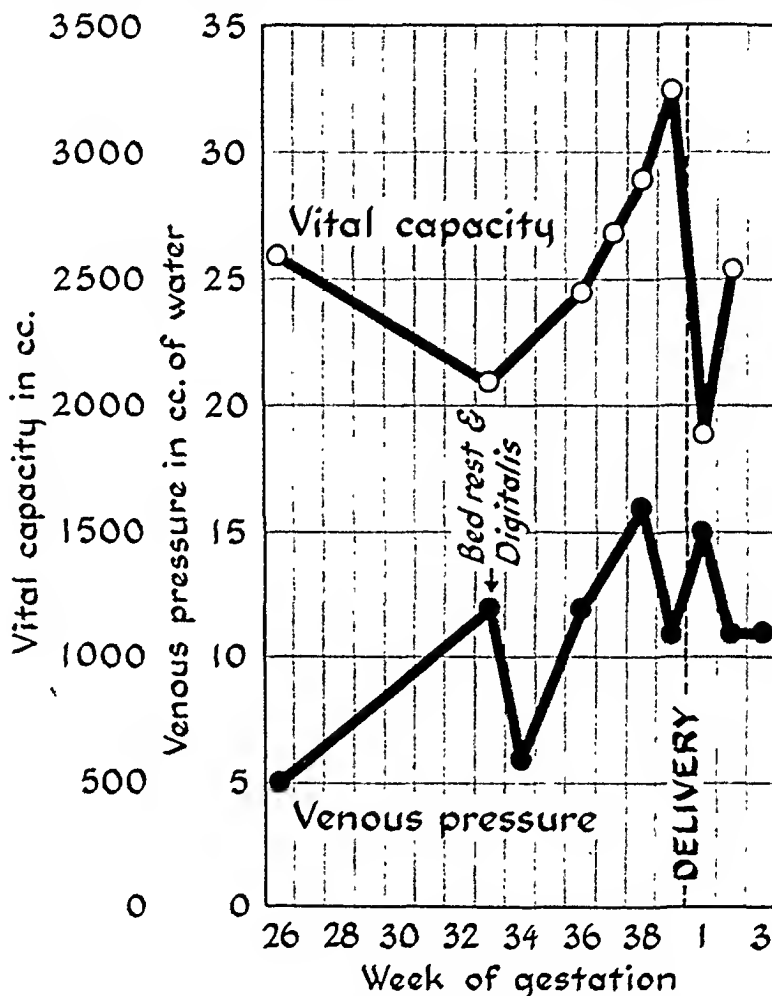


Fig. 7.—Circulation studies in congenital heart disease. Mrs. D. P. in spite of limited activity, the vital capacity decreased and venous pressure increased. There was no clinical evidence of heart failure. However, after bed rest and digitalis she improved.

Vital capacity is easy to determine. Results have been more readily obtained and more accurate since we utilized the spirometer of the ordinary basal metabolism machine. With this method it is possible to have an accurate graphic measurement for inspection. Furthermore, some notion of cooperation on the part of the patient could be seen. For example, one patient showed a sudden drop of 400 c.c., but the graph indicated it was a poor attempt. Investigation showed the patient to be dissatisfied because of prolonged hospitalization, and the record was discarded. Maximum value of this and other similar tests is obtained when observations are begun early in pregnancy and repeated at monthly intervals. Later, they may be done weekly as the load of pregnancy increases.

In a similar manner, base line values for venous pressure and circulation times were established. The tests were repeated with increasing frequency as pregnancy advanced.

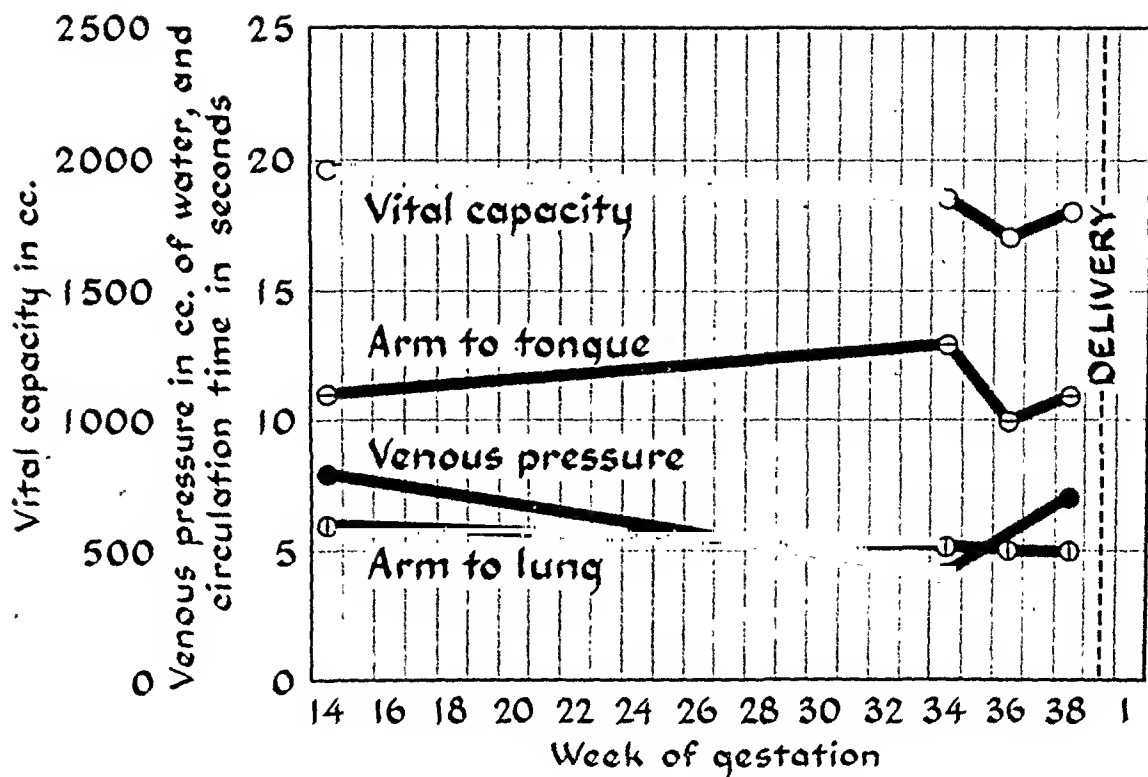


Fig. 5.—Circulation studies in congenital heart disease. This patient, Mrs. E. G., a Class 2 cardiac, went through pregnancy without event. The vital capacity, venous pressure and circulation times were normal throughout.

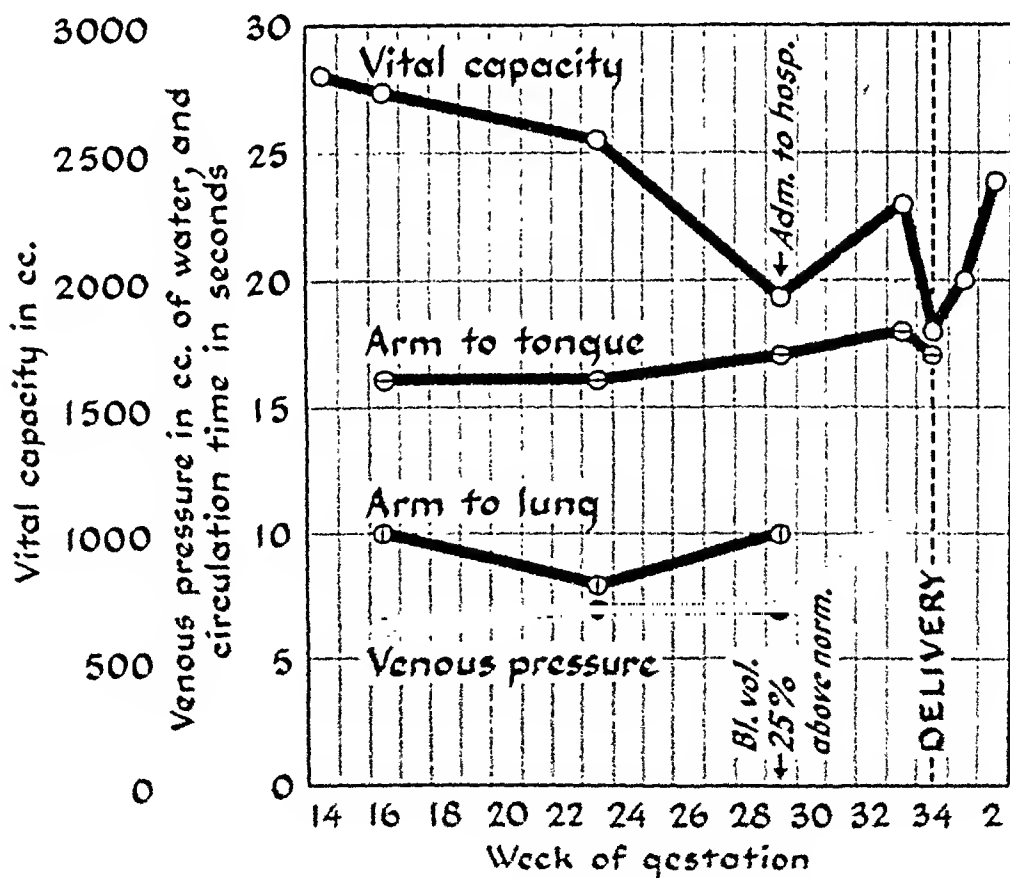


Fig. 6.—Circulation studies in congenital heart disease. Mrs. V. J. showed a decreasing vital capacity which suggested a diminishing cardiac reserve. Hospitalization and bed rest produced improvement as manifested by increasing vital capacity.

Space does not permit presentation of the detailed records of all patients. Figs. 5, 6, 7, 8, and 9 show results obtained from such measurements.

Discussion

The management of all types of heart disease in pregnancy is intimately related to the increased burdens placed upon the heart. These are but two—the inevitable and the incidental loads. The *inevitable* load comes from the augmented blood volume which increases the minute volume output of the heart, the increase in oxygen consumption as manifested by elevated basal metabolism, the strain of delivery, whether vaginal or by cesarean section, and the puerperium. The *incidental* load may come from a variety of sources such as infection, obesity, anemia, physical and mental strain, etc.

Does the pregnant woman with congenital heart disease have these same loads? Does she have additional ones? And finally, does she react to them differently than do women with rheumatic disease?

Many of the usual incidental loads were common to these patients. Some mothers were made worse by anemia or by excessive weight gain or by infection. The importance of these common complications is so well known that further comment is unnecessary.

Special mention must be made of toxemia of pregnancy. Hamilton and Thomson² and Henderson⁷ have emphasized the gravity of toxemia in mothers with heart disease. It occurs at the time of peak physiologic load and thus strikes the heart at the most vulnerable time. This study shows the gravity of toxemia in patients with congenital lesions. Five patients had patent ductus arteriosus, and both developed congestive failure after the rapid onset of the toxemia. This suggests that a rapidly developing toxemia in a person with a large congenital defect throws a burden not only on the left side of the heart, but also on the right because of the shunt through this defect. Prompt attention to the mildest toxemia is imperative and, should conservative measures fail, the patient becomes a candidate for termination of pregnancy before serious cardiac strain has had an opportunity to develop. Toxemia may be an even greater hazard in congenital heart disease than it is in rheumatic heart disease.

Most of the incidental loads can and should be recognized by careful prenatal observation, and controlled partially or completely by careful management. Need for hospital care at the slightest abnormal sign must be emphasized. It is not unusual for these patients with the serious forms of congenital heart disease to need hospitalization during the entire last trimester. In this way it is possible to reduce the incidental load at the time of peak inevitable load.

There is no symptom, no sign, no laboratory test which can give definite accurate information about the cardiac reserve of all patients. On the other hand, there are many subjective and objective findings which frequently give valuable assistance. It is important to exhaust these possibilities to the point of diminishing returns in all pregnancies complicated by heart disease to achieve a minimal maternal mortality.

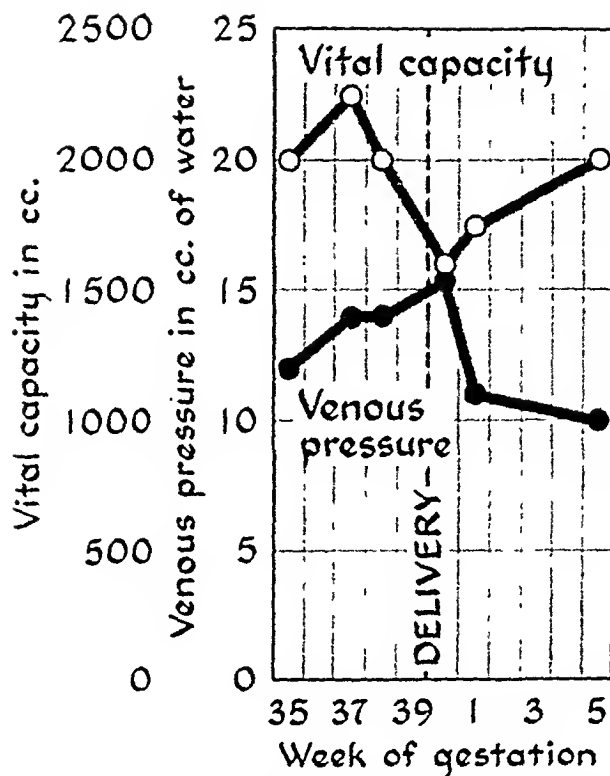


Fig. 8.—Circulation studies in congenital heart disease. Mrs. L. Y. The decreasing vital capacity and increasing venous pressure suggests that peak load was at delivery in this patient. She did not decompensate.

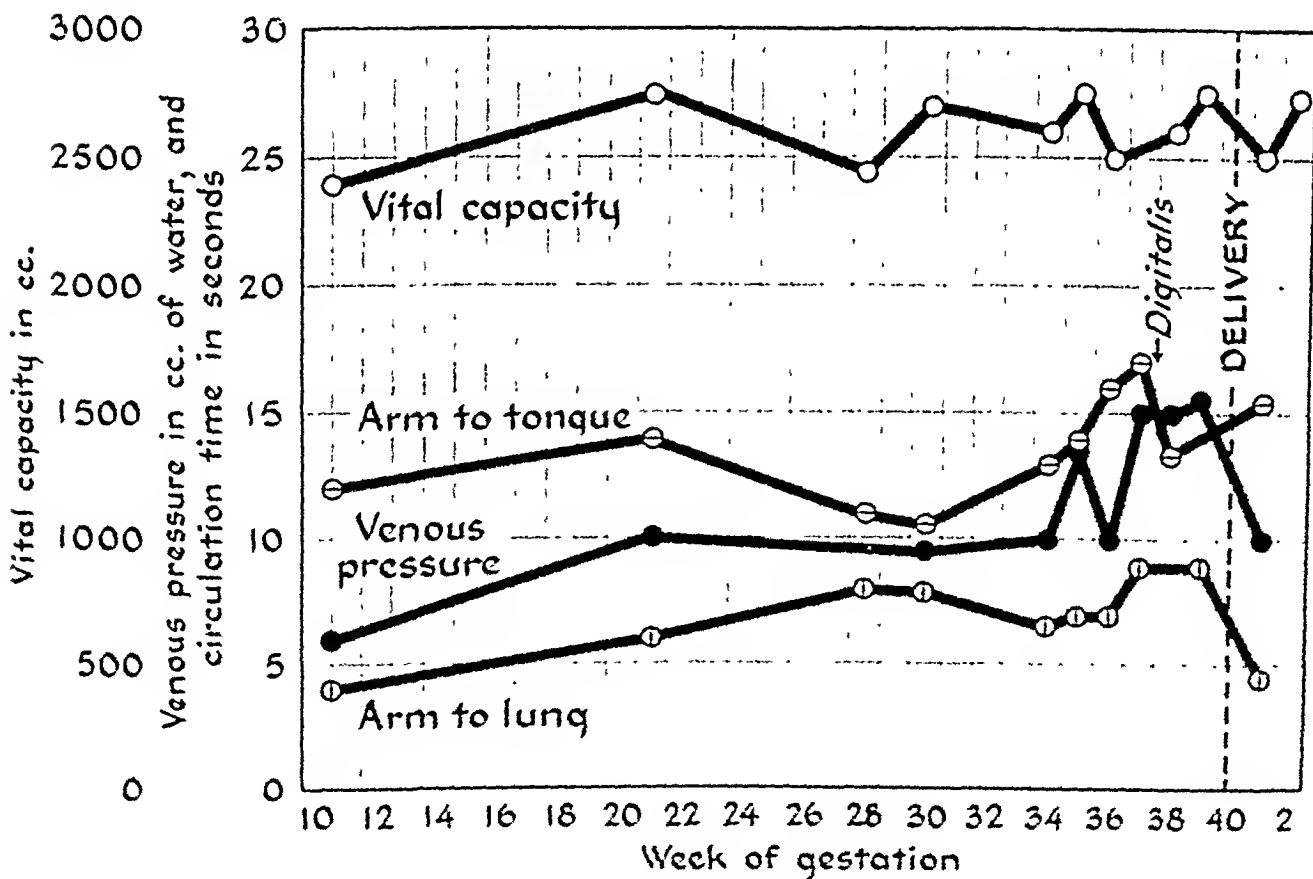


Fig. 9.—Circulation studies in congenital heart disease. Rising venous pressure and arm to tongue circulation time suggested a diminishing cardiac reserve. Some improvement followed digitalization. Vital capacity did not change.

uterus was emptied, the blood pressure dropped suddenly. All but one patient recovered, but several were in a critical condition. The nature of this mechanism is not clear, but the most likely explanation is that the sudden drop in peripheral blood pressure is accompanied by a reversal of blood flow through the congenital defect. With peripheral hypertension there would be at least temporarily an increased arteriovenous shunt, then with the shock of delivery, a reversal with the production of a venous-arterial shunt. The possibility of this mechanism was postulated by Abbot, quoted by Jensen,² who said he had never heard of an actual case reported. Hamilton and Thomson² reported three patients who died of shock following shocking operative procedures such as cesarean section and version and extraction. No detailed information as to blood pressure was given. Certainly shocking operative procedures can be a factor in this syndrome. However, similar changes happened twice in the same patient (Fig. 3), and she was delivered spontaneously with ease. The size of the defect must be important, and this was confirmed in one patient by autopsy. She had an enormous patent ductus arteriosus. Of significance, too, is the functional class. With one exception, every patient, who had the hypertension-shock syndrome, was in Class 3 or 4 at the time of delivery. There was no correlation with pulse and respiratory rate.

Just why three women with hypertension did not develop shock is not known. Perhaps it was because the lesion was small and the cardiac reserve good.

Little is known concerning therapy. Hamilton and Thomson² have suggested binding of extremities. This is worthy of trial, but we have not done so. Therapy in this series was merely supportive with oxygen, digitalis, and similar measures. Of greater importance is to watch for hypertension during labor and to be unusually cautious with operative or other shocking methods of delivery in such patients.

Finally, the data should be considered according to the anatomic lesion.

Patent Ductus Arteriosus.—This was the most serious lesion in this study. All but one of the failures and the only death were associated with this defect. Many of these patients grew worse during pregnancy, and four remained permanently worse. The syndrome of hypertension and shock at delivery was common. These observations are at variance with those of Hamilton and Thomson,² who found a patent ductus arteriosus to be less serious than a ventricular septal defect.

Ventricular Septal Defect.—This was also a serious complication, but not so serious as patent ductus arteriosus. One of this group failed and nearly died. Those with the milder forms of the disease withstood pregnancy well.

Auricular Septal Defect.—This produced no serious problems in the three patients of this group.

Pulmonary Stenosis.—Only one patient was so diagnosed, and she tolerated pregnancy without serious difficulty.

As a group, those with patent ductus arteriosus and ventricular septal defects were problems, but it is likely that the size of the lesion and the cardiac reserve are more important than the anatomic lesion.

Finally, we must give some thought to the future, particularly as it concerns the surgical treatment of congenital defects. Girls who now are having

It is not necessary to review all of these studies in detail, but the significance of some are worthy of emphasis.

We have adhered to the New York Heart Association method of cardiac classification and agree with Mendelson⁸ concerning the advantages of this method.

First, it is important to know the class before pregnancy so that it can be correlated with the type of lesion and changes of class during pregnancy. With the exception of those with patent ductus arteriosus, no Class 1 patient worsened during pregnancy. The importance of the prepregnancy class was shown in another manner. No patient failed during pregnancy or delivery if she maintained her prepregnancy class through the first six months of gestation; but every patient who deteriorated one class from her prepregnant level during early pregnancy (six months), also deteriorated one or more classes in late pregnancy. All who failed exhibited such a change in early pregnancy; and all but one had patent ductus arteriosus. Finally, there was the return of the patients to nonpregnant levels. Four failed to return to prepregnant levels. Again all of these had patent ductus arteriosus.

Of the various objective tests for showing changes in cardiac reserve, the calculation of vital capacity has been the most helpful—especially in mothers with patent ductus arteriosus. If vital capacity is compared from patient to patient, it must be done by calculations based on surface area, which, incidentally, have never been done for the pregnant woman. To obviate this difficulty, we have been content to depend upon the change in vital capacity in a given patient. It has been established that there is an increase in vital capacity during normal pregnancy.⁹ With the accuracy of the method described above, we believe, as do Hamilton and Thomson³ that a progressive decrease of more than 10 per cent may be significant.

Another patient may have no significant change in vital capacity, but increasing venous pressure, or circulation times may presage impending failure. Fig. 9 shows such pattern. As soon as a threat of failure was obtained, the patient was digitalized, activity was completely restricted, and she improved and completed pregnancy satisfactorily. Nearly everyone is aware of the errors which may invalidate these determinations. But, in spite of these drawbacks, tests occasionally help to pick the patient who is headed for congestive failure before customary signs and symptoms are present.

One of the distinct hazards for women with congenital heart was the strange sudden changes of blood pressure which frequently accompanied disease delivery. It would seem that preliminary hypertension is an essential part of the syndrome. Toxemia was frequently the cause. On the other hand, several patients had an unexplained increase in blood pressure during labor without the presence of toxemia. Regardless of cause, it would seem reasonable to expect that sudden hypertension in the peripheral circulation would be felt in the pulmonary circulation if a large defect existed either between the pulmonary artery and the aorta or between the right and left ventricles. This preliminary hypertension, present in all but one of the group under discussion, reached a peak at about the time of delivery. Then a few minutes after the

Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—The paper of Dr. Lund has reported a large series of these relatively rare cases. Very few of us have had personal experience with any large series from which to draw conclusions.

In our clinic we have had seven patients who have delivered fifteen babies. One of these patients died, the others survived. I will briefly indicate the results that we obtained in these cases. The first was a 37-year-old primipara. The disease had been recognized since she was 3 years of age. The type of lesion was not diagnosed and this woman died. Attacks of dyspnea were frequent during the pregnancy. She had a blood pressure of 146/96 and a 3-plus albumin. We hospitalized her Dec. 14, 1945, and planned to do a section four days later, but she was so much improved at that time that we waited, and this was probably a fatal mistake. The membranes ruptured suddenly on December 23 and she delivered in two and one-half hours. The baby weighed 3 pounds and survived. The mother was given oxygen during delivery and afterward, and survived the delivery in remarkably good condition. The toxemia improved, there was less albumin, blood pressure was lower, but her heart condition did not improve, and she suddenly died on Dec. 31, 1945. One might question whether she should be classified as an obstetric or a cardiac disaster. Women with congenital heart disease seldom live more than 35 years without the strain of pregnancy.

The second patient had been a blue baby. She was a primipara. She had dyspnea on exertion more or less all of her life. She had a vital capacity of 93. She had an arcuate type of uterus. She was admitted in the twenty-fourth week of her pregnancy, was kept in the hospital, and had bed rest from January 7 until March 3 and was delivered by cesarean section under local anesthesia. She and the baby both survived.

Another patient, 22 years old, had a toxemia shown by a blood pressure of 174/104 the night of the labor. There was no evidence of cardiac decompensation throughout the pregnancy. She had had scarlet fever, chickenpox, measles, whooping cough, but no endocarditis. She entered the hospital in labor with 8 cm. dilatation, and delivered spontaneously three hours later. Both she and the baby survived. She had had a previous delivery in June, 1942, the child weighing 6 pounds 4 ounces.

I will not read the other histories of patients on whom I have some notes, but will use this minute to emphasize some of the points made in the paper. As the essayist has indicated, these patients usually die of cardiac disease at a young age. Premature labor has been frequent in our experience. Induction of labor we think is questionable, because, if the induction does not succeed, a long labor under these circumstances is very bad. We believe that one should wait for spontaneous labor, particularly because if infection should be introduced by vaginal manipulation, it would not be well combatted.

Local anesthesia should be used, and one should prepare for a premature infant. The internists see few of these patients, and relatively little help can be obtained from them. This is because they have not watched these patients go through pregnancy and labor, therefore the management lies more with the obstetrician who because of previous experience knows more about how the heart will act in these cases than does the internist.

DR. BAYARD CARTER, Durham, N. C.—I would like to know how Dr. Lund classified his patients with congenital heart disease, also whether he considers patent ductus arteriosus a congenital anomaly of the heart or of the blood vessels. It would also be interesting to know the type of delivery and the form of anesthetic employed in managing these patients.

We have had during the years 1942 to 1946 the following patients with various forms of congenital heart disease:

1. Dextrocardia—two patients.

A. Negro, married, aged 29 years, para 5-0-5. No prenatal, delivery, or postpartum complications. She had two spontaneous uncomplicated deliveries in our care. She is now para 7-0-7.

a patent ductus arteriosus ligated should present no problem at the time of pregnancy; but we are apprehensive about those who are now having surgery for tetralogy of Fallot and who will wish to have babies ten years from now. Until more information is available, it would seem wise to consider these people as serious cardiac risks, and pregnancy should be undertaken only with extreme caution under constant observation.

Summary and Conclusions

Twenty-nine pregnancies have been observed in twenty-five patients having congenital heart disease. The pregnancy in general was not adversely affected. Toxemia was rather common and proved to be a very serious complication. The incidence of premature delivery was high at 27.5 per cent. Labor and delivery were never difficult, and half were described as being rapid and easy. All deliveries but two were by the vaginal route under local anesthesia.

There was one maternal death, a patient with patent ductus arteriosus and severe pre-eclampsia. There was one neonatal death—an infant with a ventricular septal defect whose mother had the same type of lesion.

The effect of pregnancy on congenital heart disease was frequently different from that on rheumatic heart disease. There was considerable variation in effect within the group according to the type of defect. Those with patent ductus arteriosus were most seriously affected. Moderate change was noted in those with ventricular septal defects, while those with auricular septal defects and the one with pulmonary stenosis were little changed.

The New York Heart Association's classification was used, and it proved to be valuable. All patients who changed from their prepregnant class to a higher class in early pregnancy went on to an even higher class later in pregnancy. All of those who failed were in this group.

The use of vital capacity, venous pressure, and circulation times were sometimes of value in predicting the development of congestive failure.

Strange changes in blood pressure at the time of delivery were found in 25 per cent of the group. The syndrome usually was manifested by hypertension reaching its peak at delivery and then sudden shock after delivery. One patient died following this reaction. The suggested explanation is a sudden shunt of blood from the right side of the circulation to the left because of drop in peripheral pressure.

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THE TREATMENT OF CERVIX CARCINOMA WITH RADIUM AND 800 KILOVOLT X-RAY*

HERBERT E. SCHMITZ, M.D., CHICAGO, ILL.

(From the Mercy Hospital Institute of Radiation Therapy and Loyola University
School of Medicine)

DURING the ten-year period of 1933 through 1942 there were 422 patients suffering with carcinoma of the cervix admitted to the gynecologic service of the Mercy Hospital Institute of Radiation Therapy. It was at the beginning of this period that higher voltage x-ray therapy was first introduced at the Institute. The plan of radium therapy has remained the same since 1924. Therefore, a direct comparison of cases for the ten years of this study with the cases previously reported would show any advantage gained by the addition of higher voltage x-rays. It has been previously shown that an increase in the x-ray dose, due to improvement in technique, has given better permanent end results.⁹

In order to obtain an accurate opinion as to the effect of such therapy on cervical carcinoma, all recurrent cases and stump cancers were eliminated. They numbered two hundred fifty-six. It is quite agreed that previous irradiation alters the reaction of tumor cells to further therapy.¹⁴ The treatment of recurrent and stump cancers will, therefore, be discussed in a subsequent presentation. This study will consider 166 cases that had no form of treatment before admission and are classed as primary.

The clinical grouping of these cases has been arranged according to the Schmitz classification¹¹ which is still in use in our clinic. The reason for our preference has been previously published and need not be repeated here.

Table II reveals 70 per cent of the cases to be in the later or unfavorable groups. It is hoped that this deplorable situation can be altered by the intensive lay educational programs now being carried on. It is our present opinion that we are seeing the patients earlier. No attempt has been made to determine the

TABLE I. CARCINOMA OF THE CERVIX, MERCY HOSPITAL INSTITUTE. 1933 TO 1942

Recurrent cases	256
Primary cases	166
Total	422

TABLE II. CLINICAL GROUPING OF CASES STUDIED*

Group I	11
Group II	37
Group III	70
Group IV	48
Total	166

*Schmitz Classification.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

B. White, married, aged 27 years, para 2-0-2. No complications in any of her three pregnancies under our care other than moderate hypertension in the third pregnancy. She is now para 5-0-5.

2. Patent ductus arteriosus—three patients.

A. White, single, aged 23 years, para 0-0-0. Elective cesarean section in first delivery (1946) for large child, small pelvis. The ductus was ligated (1947). She has imposed upon herself voluntary sterility, and we have not had the opportunity to follow her in another pregnancy.

B. White, married, aged 25 years, para 1-0-1. Uncomplicated prenatal course and spontaneous parturition (1942). Has not been seen since 1942.

C. White, single, aged 13 years, para 0-0-0. Ductus ligated in May, 1945. Uncomplicated prenatal course. Low forceps delivery at term, May, 1947. Normal course.

3. Congenital subaortic stenosis—one patient.

A. White, single, aged 19 years, para 1-1-0. Had performed elsewhere "therapeutic abortion." Seen by us in second pregnancy at eight and one-half months. Advised to go to term. Delivery elsewhere normal in all details.

4. Eisenmenger syndrome—one patient. (Dextroposed aorta overriding an intra-ventricular septal defect.)

A. White, married, aged 23 years, para 0-0-0. Admitted February, 1947, for early incomplete abortion. Induction of abortion denied by the patient. A dilatation and curettage had to be done for bleeding. Course normal. In this patient the question of tetralogy of Fallot was debated.

5. Congenital heart block—one patient.

A. White, married, aged 33 years, para 0-0-0. Seen in seventh month of first pregnancy. No complications in prenatal course. Delivery spontaneous and course uneventful.

We agree with Dr. Lund that we should classify these patients as accurately as we attempt to classify patients with rheumatic heart disease. The prenatal course should be rigorously supervised. The conduct of labor should be free of the tendency to worry too much concerning the process of parturition and should emphasize the physiology of the congenital anomaly.

DR. LUND (Closing).—The patient that Dr. Falls presented emphasizes, by her unfortunate accident, the danger of toxemia in congenital heart disease. We have a feeling that a patient with any form of toxemia should be very carefully observed and, if necessary, be considered for interruption of pregnancy.

I agree with both discussants in the importance of the obstetrician knowing about heart disease. The obstetrician must know something about the way a patient who has heart disease behaves during pregnancy and labor.

I will have to pass the question asked by Dr. Carter as to whether patent ductus arteriosus is a disease of the vessels or of the heart. We have had no patients with dextrocardia.

Most of the patients were delivered under local anesthesia. A few had gas and local anesthesia, while some had nothing.

I would like to close with this thought: We are now seeing patients, young girls, who are having surgery done for the tetralogy of Fallot. They have a severe oxygen deficiency before surgery and are left with a concentration of 75 to 80 per cent after the surgery. These patients will be bad obstetric risks when they come to us within the next ten years. They must be carefully evaluated before undertaking pregnancy.

this extension with x-ray therapy then radium is used. It has been our impression that radium therapy contributed very little in these cases if they were refractory to x-ray.

By means of the measuring frame shown in Fig. 1, an exact outline of the pelvis of the patient to be treated is obtained. The depth of the tumor is now determined by use of calipers and this information plotted into the pelvic outline previously obtained.¹² As it is our desire to attain an x-ray dose of 4,000 r into the tumor and surrounding gland-bearing areas of the pelvis, the number of fields necessary are determined. Whenever possible we use but one anterior and one posterior field. The size of the field being 20 by 20 cm. or less, depending on the size of the pelvis. We desire to irradiate an area extending from the promontory of the sacrum to the symphysis and from one anterior superior spine to the other. Using 800 K.V. x-ray with 10 M.A. at 70 cm. F.S.D. and filtering with 1 mm. lead, 1.56 mm. tin, 2.62 mm. copper, 3 mm. aluminum + 2 mm. extension chamber, we obtain 44 r per minute on the skin. At 10 cm., measured in a presdwood phantom, we receive 56 per cent of this amount.

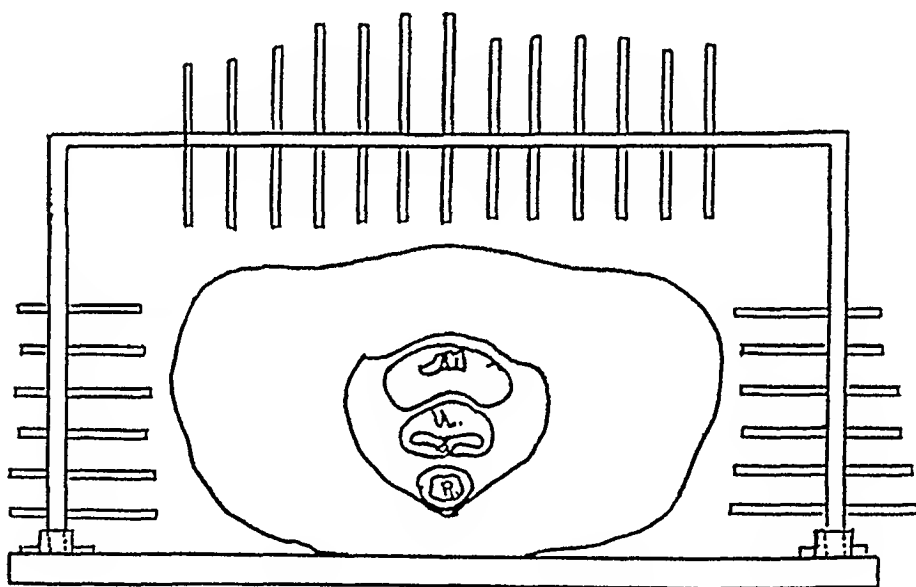


Fig. 1.—Calliper to obtain the topography of the pelvis and hips.

As our tolerance skin dose with x-rays of this intensity is in the neighborhood of 4,000 r, multiple fields are not necessary unless the patient measures over 20 cm. from anterior to posterior. If this be so, three or four fields are employed according to the need. Measurements made with a presdwood phantom using our 20 by 20 cm. field show that we lose in the neighborhood of 1 r at the outer margin of the field and with the 10 by 10 cm. field our loss is 0.4 r. This difference is so small that we prefer the massive homogeneous irradiation obtained through large ports. No special effort is made to screen out vital structures as this practice invites error due to misdirection of the radiation beam.

Although our patients experience intense discomfort at the height of the irradiation effect, the acute cystitis, proctitis, and enteritis subsided with little permanent injury to these structures. The opportunity of inspecting the pelvis in cases of endometrial carcinoma that have been irradiated similarly and then subjected to hysterectomy has revealed no significant injury to the pelvic viscera.

age or delay period in these patients as such studies have been published and the age of greatest frequency of cervix carcinoma has been established.¹¹ The delay period is directly responsible for the extent of the disease in most instances. Four of the cancers in Group I were extremely early and were diagnosed by microscopic examination of the tissue removed at biopsy. It is our policy to remove tissue for microscopic examination from all suspicious areas before any treatment is undertaken.

TABLE III. MICROSCOPIC GRADING OF TUMORS (BRODER'S)

GRADE	NUMBER	PER CENT
I	4	2.4
II	51	30.7
III	52	31.4
IV	10	6.0
Adenocarcinoma	4	2.4
Not Graded	45	27.1
Total	166	100.0

The microscopic grading of the tumors was carried out according to Broder's³ division into four grades. In 45 cases the pathologic reports did not carry a grading, and the tissue was not obtainable for review. A comparison of the remaining cases with the incidence of the three varieties of Martsloff,⁶ which he gives as 15 per cent spinal cell, 66.8 per cent transitional, and 12.0 per cent spindle cell shows a slight difference. The middle groups or transitional cell type is about the same. We have frequently obtained different gradings from repeat biopsies of the same tumor and, therefore, have learned to expect variations. Adenocarcinoma was found in 5.4 per cent of Martsloff's series, while our incidence was 2.4 per cent. A previous study from our clinic showed a similar incidence. As to the influence of the cell type on survival rates or response to therapy, we are not convinced that it is as important as the clinical grouping. It is our policy to treat all cell types with x-ray and radium and to reserve the Wertheim operation for those cases that are refractory to irradiation or that recur. None of the cases in this series were treated by subsequent surgery because of recurrence.

Plan of Treatment

Both radium and x-ray are employed in the treatment of all cases in the first three clinical groups. In Group IV cases, x-ray is administered, as a palliative therapy and radium withheld entirely unless the tumor regression is marked and further therapy is thought to be advantageous. It is our policy to withhold radium in those patients showing bullous edema or definite invasion into the rectal or bladder mucosa. Routine cystoscopic and proctoscopic examinations are necessary to reveal such pathology and to diagnose other pathological conditions in the urinary tract which later may be accredited to the therapy. Pomeroy⁸ found abnormal pyelographic findings in 16.2 per cent of 271 cases in which intravenous pyelographic examination was made before treatment of patients with carcinoma of the cervix uteri. If future examination reveals regression of

Results

Table IV tabulates the five-year survivals in the cases treated by this technique. Seven cases in Group III have been lost to follow-up. The condition of the patient at the time of her last visit was such in each instance that we believe they all succumbed to the disease and we have, therefore, counted them as dead in determining our survival rate.

TABLE V

CLINICAL GROUP	1924-1929*					1933-1942				
	I	II	III	IV	TOTAL	I	II	III	IV	TOTAL
Total number admitted	23	36	100	116	275	11	37	70	48	166
Total five-year good end results	21	19	30	7	77	10	27	30	5	72
Percentage five-year good end results	91.3	52.78	30.0	6.04	28.0	90.90	72.70	42.85	10.43	43.37

*Schmitz, H.: Radiology 23: 548-550, 1934.

Table V compares this group of patients to a group previously reported. They received similar radium therapy but lower voltage x-ray. The improvement in the survival rate is, undoubtedly, due to the higher voltage x-ray in present usage.

TABLE VI. TEN-YEAR RESULTS, 1933 TO 1937

CLINICAL GROUP	I	II	III	IV	TOTAL
Total number	3	17	30	19	69
Total ten-year results	2	9	9	0	20
Percentage ten-year good end results	66.66	52.94	30.0	0	28.98

Sixty-nine of the 166 cases were treated before 1937 and can, therefore, be studied for a ten-year period. The death in the Group I case was due to coronary heart disease seven years after treatment. At autopsy no residual carcinoma was found. In Group II one patient died of metastases to the lungs six years after primary treatment. Autopsy failed to reveal residual carcinoma in her uterus. A second patient was lost track of after remaining free of symptoms for eight years. In Group III one patient suffered a fractured hip (not pathologic), and died of complications as a result of this seven years after her original therapy. Two other patients were lost track of in the sixth year having been free of demonstrable disease until this time. Two other patients died of recurrence in the fifth and ninth years, respectively. In Group IV one patient died of recurrence in the seventh year and two were lost to follow-up, one in the seventh year and the other nine years after therapy.

Discussion

The technique of radiation as described varies somewhat from the most widely accepted procedures because of the method of applying radium and x-rays and the dosages used. This has helped us to avoid the numerous complications of bowel, ureteral, and bladder injury described in many clinics and given by some as a most important reason for returning to surgical treatment. That the method is as effective is shown by the five-year relative cure rate of 43.37 per cent. Baschke and Cantril,¹ using x-rays of similar intensity administered through four 10 by 10 cm. fields and a radium dose of 4,000 mg.

Radium therapy is carried on in conjunction with the x-ray therapy unless the condition of the cervix due to the malignancy is such that radium insertion would be difficult. Then the radium application is postponed until such a time as the tumor has regressed sufficiently to make less difficult the radium insertion. Fifty milligrams of radium filtered with 2 mm. brass and 3 mm. of para rubber is placed in the cervical canal for thirty hours. This dose is repeated at seven-day intervals for a total dose of 4,500 mg. hours. The placement of the radium in the capsule is so arranged as to irradiate the entire cervix from the internal os to the external os. The depth of the uterus is determined before each insertion and the length of the capsule adjusted accordingly.

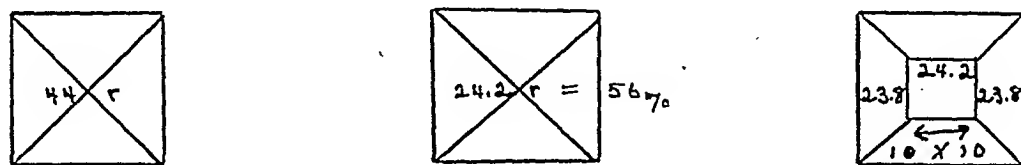


Fig. 2.—800 K.V.—10 Ma.—70 CM. F.S.D.

Filters Pb. 1.0 mm.

Sn. 1.56 mm.

Cu. 2.62 mm.

Al. 3.0 mm.

Extension Chamber 2.0 mm.

Size of Field 20 x 20 cm.

In Air—36 r

Surface with Backscatter

10 cm. depth

10 cm. depth

Further radium is occasionally used in the form of needles or a plaque against the cervix if regression has not been satisfactory. Such dosage is controlled by the size and location of the refractory area and in this group has never exceeded 1,500 mg. hours. If we accept the lethal radiation tissue dose for carcinomas of 5 to 7 E. D. as given by Wood and Prime¹⁵ or 10 E. D. for squamous cell cancers and 2.5 E. D. for transitional cell cancers, as reported by Martin and Quimby,⁵ we may assume that this combined radium and x-ray dose is adequate to destroy most squamous cell carcinomas for a distance of 3 cm. in all directions from the cervical canal. Sensitive cell types may be destroyed out to the limits of the bony pelvis. We rely entirely on x-ray therapy to destroy extension of the disease beyond the zone of effective radium rays. That certain cell types respond to this therapy is evidenced by survivals in clinical Groups III and IV and by the observation of Morton⁷ that there were four times as many lymph gland metastases in nonirradiated patients. The five-year comparison of end results has influenced our decision not to increase the radium dose by applications against the cervix or to the fornices. Our low incidence of major complications, we believe, to be due to this fact.

TABLE IV

CLINICAL GROUP	I	II	III	IV	TOTAL
Total number admitted	11	37	70	48	166
Total five-year good end results	10	27	30	5	72
Percentage five-year good end results	90.90	72.70	42.85	10.43	43.37

cedures are warranted, we believe, when radiation has failed. Surgery as extensive as this is relatively safe due to present-day methods. However, the end results will have to be studied before the procedure can be correctly evaluated.

The large number of recurrent cases in our series was due to the installation of higher voltage irradiation; many cases were referred because of failure of lower voltage x-ray so that higher voltage x-ray might be evaluated. Such material would not be referred to a surgical clinic and we, therefore, feel that these cases must be eliminated for comparative study. Of the 166 cases only 22.2 per cent were clearly operable (Groups I and II). However, according to Victor Bonney's² present indications for operation, many of our Group III cases would still fall into his operable group. The incidence of operability would still fall short of his 50 per cent. Our salvage in the Groups I and II cases was 70 per cent at the end of five years and 55 per cent for ten years. This is higher than for any comparable surgically treated group. Leclerc⁴ had 59 per cent five-year survival with an operative mortality of 8.5 per cent in Group I (League of Nations) cases treated by Wertheim hysterectomy and Bonney 53 per cent in 300 cases in which there was no lymph node involvement. It is our decision, therefore, to continue treating all cases of cervix cancer with irradiation and to employ surgery for the conditions as stated.

Summary

One hundred sixty-six cases of primary carcinoma of the cervix admitted during the ten-year period of 1933 through 1942 are grouped clinically and graded microscopically.

The method of combined radium and x-ray therapy is described.

The five- and ten-year survivals have been determined and the advisability of combined surgical and radiological therapy is discussed.

The survival rate obtained in the Group I and II cases of this study are compared with reported series of surgically treated cases.

The evidence presented is in favor of continued radiological treatment of cervix cancer.

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hours through a cervical tandem and 4,000 mg. hours given through para-cervical applicators, report a relative cure rate of 43 per cent, but warn against the use of the radium treatment during or following the course of roentgen therapy "as the rectal and intestinal complications are apparently more severe." Our experience with transvaginal x-ray therapy has been disappointing because of the difficulties associated with insertion of the rigid x-ray cone into an abnormal vaginal tube. We have, therefore, given up its use. It appears to us that radium and x-ray in safe dosage will destroy cancer within the region of the cervix in most instances (80 to 90 per cent). If the growth has extended into the para-cervical areas, this cure rate drops to 52 to 56 per cent, the failures probably occurring in those cases with unrecognized lymph node metastases or extremely resistant cell type. It is in these instances that the Wertheim operation is indicated but present reports are not convincing enough to warrant its substitution in all Group I and II cases. Many of these patients would not meet the requirements for safe surgery and, therefore, the operative mortality rate would nullify the increased salvage. When the radium dose is increased the same situation results. The increase of complications is so marked that the salvage is not increased.

An attempt to follow our cases through the second five years was unsatisfactory although the absolute ten-year survival rate is 28.98 per cent. The age of these patients increases the death rate from all causes and it is more difficult to keep the patient coming to the clinic. That patients can have recurrences after five years is definitely shown in three cases that we know to have succumbed to recurrence of the disease after five years. That these losses could have been avoided by surgical measures employed after irradiation is questionable because the patients lost were in Groups II, III, and IV at the time of treatment and, therefore, not suitable for surgical procedures. In these cases the tumor cells are arrested for various lengths of time because of the inability of the cell to be active in the altered surroundings produced by the action of the x-rays and radium on the tissues. "If the tumor surroundings are so altered (fibrosclerosis) that the nutritive effect of this change cannot be overcome by the adaptability of tumor cells in successive generations, the tumor growth will finally stop and the cell strain will die (Clinical Cure)." (Windholtz¹⁴.) However, if the tissues recover then the cell again becomes active and recurrence results.

The microscopic grading of tumors is an aid in predicting the response to therapy but not in determining the type of treatment indicated. A localized tumor irrespective of its cell type should be irradiated as in most instances it will respond satisfactorily. If it proves to be resistant to this form of treatment, surgery can be instituted and executed without increased difficulty. As the present time we are reserving the Wertheim hysterectomy for those cases proving to be resistant to our dosage of x-ray and radium as evidenced by persistence or recurrence of the lesion. In some instances where the extent of the disease has warranted such a radical procedure, we have combined the Wertheim hysterectomy with abdomino-perineal resection of the rectosigmoid. This permits thorough cleaning out of the entire pelvis. Such radical pro-

Dr. Schmitz' report demonstrates:

1. The value of external roentgen therapy in addition to radium application in the treatment of cancer of the cervix.
2. The superior results of 800 kilovolt therapy over lower frequencies.
3. Irradiation should be administered to the limit of tolerance regardless of the histologic type or the size of the lesion.
4. Clinical grading is of greater prognostic value than cell typing.
5. Early diagnosis and treatment affect salvage more than any technical improvements that have yet been offered.

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—It is apparent from the physical properties of x-rays that, properly filtered, the so-called supervoltages, that is, voltages higher than the conventional 200 or 400 kilovolts, allow delivery of higher dosages to the depths of the pelvis without extreme skin injury. The aim in reporting series of patients such as this is to indicate the effectiveness or not of x-rays of this quality and amount delivered to the cancer-bearing areas. The figures just presented of five- and ten-year arrests are impressive. We are fortunate to have a report such as this from a group long experienced and interested in the treatment of cancer.

A point to be emphasized again in cancer reporting is that follow-up of patients with all its expense and difficulty is a very important thing since untraced patients are properly counted as dead of the disease. The author had good results in this series, notwithstanding having lost trace of seven patients of the 166, fortunately with enough final information about each to justify their inclusion as having succumbed to the disease. A few years ago in Cleveland, Dr. Lawrence Pomeroy attempted to establish some difference in results between four 200 kilovolt and 400 kilovolt machines used at different places in the city. He found it most discouraging to trust figures from public clinic groups with their shifting population and no efficient follow-up systems. Any group devoted to cancer therapy with a more or less personalized follow-up system can show much better results than others no matter what type of machine. If there is no other reason, adequate follow-up is an argument for specialized hospitals for the treatment of cancer, such as the author represents.

There is a personal sense of disappointment that the author has abandoned the vaginal cone method of therapy. From a limited experience it has been felt the development of this method might allow further reduction in radium dosage with consequent less reaction, immediate and remote, than now attends therapy of cancer of the cervix with radium and x-ray.

None of this series of patients was operated upon. The relegation of the Wertheim operation to recurrences and some patients not doing well with x-ray has interesting implications. Results of such operations will be looked for with interest in the future.

DR. GEORGE GRAY WARD, New York, N. Y.—Dr. Schmitz has shown the value of the very high voltage machine. At the Woman's Hospital we have only a 200 kilovolt machine.

The employment of the high voltage x-ray by the fractional technique in conjunction with the radium therapy has proved of definite value, and is generally employed. In the deep-seated lymphatic glands in the higher pelvis, however, the x-ray is not always effective. Hence the value of Taussig's procedure, or the extraperitoneal gland removal technique.

The results obtained by Belney and others using high voltage x-ray applied directly to the cervix with a vaginal cone apparatus promises much. It has not been in use a sufficient length of time as yet to evaluate it properly. We have been using this technique lately on a few cases.

The extent of the disease must be appraised to make a prophylactic probability. This is based on the clinical findings and does not permit us to know the actual extension of the carcinomatous involvement.

It is difficult to determine whether the parametrial infiltration is inflammatory or carcinomatous. Also it is not possible to demonstrate carcinomatous lymph nodes in the

Discussion

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Although x-rays of as high voltage as 1,000, and even 2,000 kilovolts, are being used in some clinics, comparatively little information regarding the end results of this therapy in the treatment of carcinoma of the cervix is available. Leucutia claims 50 per cent five-year survivals with 400 kilovolts, as compared to 19 per cent with 200 kilovolts. Holmes and Schultz report 26 per cent five-year arrests, stages not noted.

The value of a report such as this is always enhanced by a description of the physical factors involved, as Dr. Schmitz has given us. His measurement of patients and calculation of dosage is similar to that employed by us at the Philadelphia General Hospital. Unless the dosage is determined precisely, one cannot administer x-ray therapy in adequate dosage, with the assurance of avoiding serious damage to normal tissues. It is quite apparent that since some of the rays are absorbed by the tissues through which they pass, a woman with a thick abdominal wall will require more external irradiation to administer the standard tumor dosage than would a patient with a thin abdominal wall. To avoid damage to the skin or vital organs, this may require the use of additional ports. It is my impression that we gynecologists have many times been derelict in failing to provide these data concerning the factors employed in our radium and x-ray therapy.

We also prefer and employ the Schmitz classification. I should like to emphasize Dr. Schmitz' point that in Stage IV cases x-ray therapy alone should be given. Following this, however, a number of lesions will become suitable for radium application.

In our clinic we use the four port technique, believing that thereby we avoid intensive irradiation of the bladder and rectum, as would be the case if one large anterior and one large posterior field were utilized. We credit this technique with the infrequency of serious damage to the intestinal tract in our experience. Del Regato employs the Trendelenburg position for his patients during treatment to avoid intestinal injury. It must also be remembered that with higher voltages a greater percentage of the irradiation passes, *unabsorbed*, through the tumor area to the normal tissues beyond. This so-called "exit dose" is great enough to be troublesome when it falls on the same area as the irradiation from the opposite field. It would seem that crossfire from three fields, whose paths do not overlap, might avoid some of the "exit dose" complications encountered in the use of the higher voltage.

Our experience with transvaginal high voltage therapy in carcinoma of the cervix has been so satisfactory in clearing up infection of the cervixes, and in rendering the later intra-cervicouterine application of radium easier, that I was surprised to learn that Dr. Schmitz has discontinued this form of therapy. By utilizing cones of various sizes we have had no difficulty in centering the cone over the lesion. A periscope attached to the cone-adaptor enables us to confirm its position in relation to the lesion at any time. When cone therapy is used the lower voltages are considered more effectual and less likely to cause intestinal damage.

The end results here reported are so much superior to those obtained with lower voltages, as well as Dr. Schmitz' earlier series (Table V) where 200 kilovolts were used, that one cannot deny the superiority of 800 kilovolt x-ray therapy in conjunction with radium therapy, both in adequate dosage, in the treatment of carcinoma of the cervix.

How much the voltage can be increased advantageously is questionable. There would seem to be a limit to which the voltage or frequency can be increased without endangering the surrounding tissues, due to the high exit dose produced. Only the rays which are absorbed by the atoms of the tumor tissue affect the carcinoma. With higher frequencies the percentage of rays passing through the tumor unabsorbed is greater, thereby increasing the dosage to tissues around the tumor and to the skin.

Unless it is assumed, as claimed by Maisin and Estas, that rays of shorter wave lengths possess more energy and are more lethal to cancer cells than the same number of roentgens of lower voltage, it would seem from the point of view of the physicist that, with our present technical knowledge, voltages in excess of 800 or 1,000 kilovolts are of questionable advantage in the treatment of this disease.

DR. SCHMITZ (Closing).—I wish to thank Dr. Behney for bringing out the factor which we believe is responsible for our improved end results, and this is the fact that we are giving 12 per cent more radiation in the midpelvis and with the shorter, more rapidly traveling rays we are producing more destruction.

Relative to Dr. Faulkner's remarks about follow-up in these cases, it is one of the most important features of this type of work. We have a very definite plan of follow-up which time does not permit us to discuss at the present time.

Because of a fixed tube head on our 200 kilovolt apparatus we have had great difficulty in attempting transvaginal irradiation. Since having discussed the method with Dr. Behney I shall attempt it again. I can understand its value.

I am very much interested in Dr. Ward's remarks but I must disagree with the statement that irradiation has no effect on the tumor cells that have invaded the surrounding lymph nodes. Dr. Morton has shown in his studies that he found fewer invaded nodes in those cases treated with x-rays than in the cases that were not irradiated. Relative to the inflammatory invasion being mistaken for tumor invasion, that is true but we will err both ways so that in the end results it will be compensated for.

higher pelvis by palpation. This impossibility makes doubtful the prognosis of a cure but justifies a therapeutic test by irradiation. The average cure rate by radiotherapy is about 25 per cent of all cases applying for treatment with a primary mortality of from 1 to 2 per cent. In a number of clinics this rate has recently been improved.

In the last report of the League of Nations on the results obtained by radiotherapy, which was collated in 1939, an analysis of 10,970 patients in all stages of the disease treated in European and American clinics showed a five-year cure rate of 26.7 per cent, and in the 1280 Stage I cases the cure rate was 56.1 per cent.

In the Woman's Hospital we have been treating carcinoma of the cervix with radiotherapy since 1919. Up to Jan. 1, 1947, we have seen approximately 1,045 cases. We have treated to 1940 inclusive and followed for five years or more 827 cases.

We have published six statistical reports of our results showing an improvement in the relative five-year cure rate as follows:—1925—23.6 per cent
1928—23.1 per cent
1930—25.5 per cent
1932—24.8 per cent
1934—25.28 per cent
1937—28.5 per cent.

Our seventh report recently compiled and not yet published is of cases seen from 1933 to 1940, of which there were 236 seen, 217 being treated, with a five-year absolute survival rate of 32.2 per cent, and a relative rate of 35 per cent.

In the League of Nations Stage I cases, the absolute rate was 57.1 per cent, and the relative rate 61.5 per cent.

In the League of Nations Stage II, III, and IV the survival rates were absolute 24.4 per cent, and relative 26.6 per cent.

The primary mortality was 1.28 per cent.

There were fifteen stump cases (following hysterectomy) in the 236, or 6.4 per cent, with a five-year salvage of 46.7 per cent.

I will close with repeating Professor Regaud's warning: "It is necessary to have much experience to obtain from this method of treatment all the good that it may give without the evil that it may do."

DR. SUBODH MITRA, Calcutta, India.—I thank Dr. Schmitz for assuring me that a high voltage treatment is very good in giving us a high rate of salvage. As a matter of fact, I have come to this country to study the work of radiotherapists and to acquire the best information which I can utilize in treating my cases with the million-volt x-ray apparatus.

Out of Dr. Schmitz' four hundred and odd cases he had a salvage of 65 out of his 132 primary cases. I doubt whether the results can be taken as an absolute rate.

Another point: Dr. Schmitz has given the operability rate at 22 per cent. Certainly it is too small a percentage. Mr. Bonney has 61 per cent operability rate and I have 57.6 per cent.

So far as radiation treatment is concerned, we know that there is an optimum dose. You cannot improve results by increasing the radiation; on the other hand, you may do much more harm. So there is a limitation for this irradiation treatment. You cannot do anything in relapse cases.

One point I should like to emphasize, that it is high time that the fight for the supremacy of irradiation over operation should come to an end.

As a gynecologist I find practically identical results with operation as with irradiation. It is very difficult to say which method is better, but perhaps the ideal would be to have two methods instead of one so that one or the other can be utilized.

deliveries in women having section scars. From Jan. 1, 1928, to Dec. 31, 1935, there were thirty-nine (22.0 per cent) such deliveries, whereas from Jan. 1, 1936, to Jan. 1, 1947, the total rose to one hundred thirty-eight (78.0 per cent). One might hastily attribute this rising incidence in more recent years to a corresponding increase in the frequency of cesarean section. A survey of the hospital statistics, however, demonstrates a distinct, even though slight, decline in the frequency of hysterotomy in the latter period.

TABLE I

Number of deliveries following cesarean section	1x	2x	3x	4x	5x	6x	Total
Number of patients	77	30	7	2	1	1	118
Total of deliveries	77	60	21	8	5	6	177

These deliveries were distributed over the period under investigation as follows:

TABLE II.

Year	1928	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	19 yrs.
No. of deliveries	4	0	6	2	7	12	6	2	11	17	10	11	11	19	13	14	9	13	10	177

This encouraging trend can be attributed to two major developments in clinic policy during the latter period; first, the adoption and wider employment of x-ray pelvimetry during the course of labor in cases of mild pelvic contraction and uterine inertia, enabling the more intelligent interpretation of progress during labor, and second, the greater consideration directed toward successful pelvic delivery following hysterotomy. During the past eleven years such deliveries alone have been responsible for a reduction of some 12.5 per cent in the total number of cesarean sections that would have resulted, had the presence of a uterine scar been considered an absolute indication for a repetition of the operation.

A large proportion of these patients (70 per cent) were delivered by forceps application after full dilatation of the cervix to avoid the expulsive stage, thereby minimizing the stress upon the uterine cicatrix.

TABLE III. TYPE OF DELIVERY

SPONTANEOUS	LOW FORCEPS	MID- FORCEPS	LOW FORCEPS FOLLOWING SCARZONI MANEUVER	LOW FORCEPS FOLLOWING MANUAL ROTATION	BREECH EXTRACTION
50-27.9%	112-62.6%	1	7	5	4

Sixty-eight (38 per cent) of these deliveries concluded the second pregnancy in patients whose first pregnancy was terminated by hysterotomy, so that for all practical purposes this group was subjected to what should be considered as a primiparous labor excluding the second stage. No disastrous sequelae were observed as a result of this policy, contrary to the opinion¹ that the long and tedious labor allegedly inherent in a primipara is to be avoided in the patient having had a previous cesarean section. The average duration of labor for the entire group was nine hours, twenty-five minutes. The average for deliveries through the primiparous cervix was fourteen hours, twenty minutes, the shortest such labor being four hours and the longest sixty hours. The multiparas averaged six hours, twenty-one minutes, the shortest labor being one-half hour, while

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PELVIC DELIVERY FOLLOWING CESAREAN SECTION*

DANIEL H. HINDMAN, M.D., BOSTON, MASS.

*(From the Boston Lying-in Hospital and the Department of Obstetrics,
Harvard University Medical School)*

IT IS readily understandable that in an era when cesarean section was reserved for cases of marked cephalopelvic disproportion there should arise the oft-repeated dictum "Once a Cesarean, always a Cesarean." However, with the rapid progress in the development of aseptic, surgical technique and the introduction of potent chemotherapeutic agents, there has appeared a most gratifying decrease in the maternal mortality and morbidity accompanying the procedure, and an all too prevalent impression that the operation is both simple and safe. Consequently, it is not surprising to note the ever increasing incidence of the operation and the widening of its scope of application to such obstetric complications as placenta previa, premature separation of the normally implanted placenta, uterine inertia, and abnormal fetal presentation, not to dwell on the lengthy roll of questionable indications to be found in the literature. Regardless of what opinion one may possess toward the various indications, there nevertheless has come into being a not inconsiderable group of women, free from pelvic contraction and deformity, who have previously been subjected to cesarean section for some temporary consideration.

It is concerning this category of patient that we wish to dwell in some detail. The woman who has had a pregnancy terminated by hysterotomy and presents herself in a subsequent pregnancy creates a definite clinical problem and challenge. "To what degree is such a patient endangered by the presence of a scar in her uterus?" "What is the prospect for delivery through the natural birth canal in a succeeding pregnancy?" In spite of its significant practical consideration, the literature is meager concerning observations and study of pelvic delivery following cesarean section.

During the interval from Jan. 1, 1928, to Jan. 1, 1947, there have been effected at the Boston Lying-in Hospital one hundred seventy-seven deliveries through the natural birth passage in one hundred eighteen patients who had previously been subjected to cesarean section. Thirty of these women were delivered twice subsequent to hysterotomy, seven three times, two four times, one five times, and one six times, respectively.

It becomes readily evident from the above that during the past eleven years there has been a definite and steady increase in the number of pelvic

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As one would anticipate, the great proportion of these patients had been subjected to cesarean section for a temporary indication. The frequency of hemorrhage as an indication corresponds well with the high incidence of the classical type cesarean previously mentioned. This type of operation is the one employed in our clinic for cases of placenta previa and partial premature separation of the normally implanted placenta.

TABLE VIII. INDICATIONS FOR PREVIOUS CESAREAN SECTION

INDICATION	NO. OF DELIVERIES	NO. OF PATIENTS
Placenta previa	51 = 28.8%	31 = 28.5%
Premature separation of placenta	28 = 15.8%	16 = 13.5%
Uterine inertia	27 = 15.2%	19 = 16.1%
Cephalopelvic disproportion	26 = 14.7%	19 = 16.1%
Pre-eclampsia (severe)	12 = 6.8%	9 = 7.6%
Eclampsia	9 = 5.1%	4
Fetal distress	4	3
Prolapsed cord	3	2
Face presentation	2	2
Primiparous breech	1	1
Obstructing pelvic tumor	1	1
R.H.D.-M.S. and M.I. (early decomp.)	2	1
Hydrocephalus	3	1
Chorea	1	1
Varicosities of vulva	1	1
29-year-old primipara	2	1
Unknown	3	3
Total	177	118

Many of the cases of cephalopelvic disproportion were sectioned elsewhere or were delivered of infants considerably smaller than those for which they had been subjected to operation. It is most unfortunate that hydrocephalus, chorea, or elderly primiparity should ever appear in any roll of indications for cesarean section. If at the age of twenty-nine a woman is to be considered old, then certain physicians are soon to become quite unfamiliar with the mechanism, the ease, and the safety of pelvic delivery.

In more recent years it has become our policy to examine the uterine cavity immediately following the third stage of labor in every instance as a safeguard against any symptomless rupture that may have occurred in the uterine scar. The details of this aspect and the method employed in this clinic shall be discussed later.

TABLE IX

	NO. OF DELIVERIES	NO. OF PATIENTS
Exploration of uterine cavity	112 = 63.3%	83 = 70.3%
Not explored	65 = 36.7%	35 = 29.7%
Total	177	118

In spite of the fact that the uterus was explored manually in 112 cases only four patients in the entire group experienced a febrile convalescence, all of them mild in character. One patient whose uterus was not explored had a temperature of 100° to 101° F. during the first seven postpartum days, due to a mild sapremia. A second patient, who entered the hospital two days following

TABLE IV. DURATION OF LABOR

	PRIMIPAROUS CERVIX	MULTIPAROUS CERVIX	ENTIRE GROUP
Average duration of labor	14 hrs. 20 min.	6 hrs. 21 min.	9 hrs. 25 min.
Shortest labor	4 hrs.	30 min.	30 min.
Longest labor	60 hrs.	36 hrs.	60 hrs.

TABLE V. TYPE OF SECTION

	NO. OF DELIVERIES	NO. OF PATIENTS	
Classical	104 = 59%	66 = 56%	
Kerr	36 = 20%	24 = 20%	
Kroenig	10	9	a) { Classical
Latzko	7	3	
Water's	2	2	b) { Classical
Vaginal hysterotomy	2	1	
Multiple sections	4	4	c) { Classical
Unknown	12	10	
			d) { Classical
			Kerr
Total	177	118	

TABLE VI

SECTION PERFORMED AT	NO. OF DELIVERIES	NO. OF PATIENTS
Boston Lying-in Hospital	95 = 53.6%	60 = 50.8%
Other hospitals	82 = 46.4%	58 = 49.2%
Total	177	118

TABLE VII. CONVALESCENCE FOLLOWING SECTION

	NO. OF DELIVERIES	NO. OF PATIENTS
Afebrile	103 = 58.2%	72 = 61.0%
Febrile	42 = 23.7%	23 = 19.5%
Unknown	32 = 18.1%	23 = 19.5%
Total	177	118

the longest was of thirty-six hours' duration. Undoubtedly the reduction from the usually accepted statistics of primiparous and multiparous labors is to be attributed in some measure to the frequent elimination of the second stage of labor.

One hundred four (59 per cent) of the deliveries were in patients who had previously been subjected to the classical type of cesarean section, while thirty-six (20 per cent) occurred in women upon whom the low transverse (Kerr) type of section had been performed. Four patients, each of whom had experienced two previous hysterotomies, were each delivered once subsequently through the natural birth canal.

Approximately one-half of these patients had been operated upon in our own clinic, while an almost similar number were attended by their own physicians or at other clinics. For theoretical and practical considerations one would prefer to limit such deliveries to gravida who had been cesareanized in their own clinic for a temporary indication, and who had enjoyed an uncomplicated, afebrile convalescence. Even superficial inspection of the accompanying data will reveal that these criteria were not rigorously adhered to, fortunately, without development of any complications that could be attributed to such leniency.

It is only proper that the foregoing data be interpreted along with a consideration of whatever hazards may accompany attempts at delivery through the natural birth canal following previous cesarean section. The fundamental question, of course, revolves about the behavior of the uterine scar in subsequent pregnancies, whether it shall prove adequately firm to tolerate the distention of the uterus as pregnancy advances, and to withstand the stress of labor itself. The functional strength of the scar is intimately dependent upon the histology of wound healing in the uterus and the location of the incision. It is for this reason that a number of authors, during the past thirty years, have applied themselves especially to the anatomic study of these scars. There still appears to be considerable enthusiasm existent in the controversy as to the exact nature of the reparative processes taking place in the healing of the uterine incision.

J. Whitridge Williams,² from a detailed study of uteri which had been subjected to one or more cesarean sections, noted that the old scar was invisible in most instances or could be identified at most by the presence of shallow vertical depressions over the external and internal surfaces of the anterior uterine wall. This observation has been confirmed frequently by Audebert,³ Losee,⁴ Eardley Holland,⁵ and others. In more recent years, there have appeared reports of similar findings in studies directed to the scar in the lower uterine segment. Phaneuf⁶ was unable to identify the cicatrix as such in forty-one repeat lower segment cesarean sections, whereas Fuchs⁷ found it impossible to visualize the scar in thirty-three of forty-six cases upon which he performed a second cervical hysterotomy. Corroboratory observations have been made by Wetterwald⁸ and DeLee, Nadelhoffer, and Greenhill.⁹

In 1895, von Baumfurowald, Shauta, and Brann¹⁰ reported complete muscle regeneration in the scar following a cesarean section. More significant was Williams² reiteration that microscopical examination of tissue removed from the site of the incision revealed complete absence of fibrous tissue in the uterine wall, demonstrating that the uterus, just as all other organs containing non-striated muscle, heals by complete regeneration of muscle fibers and not by fibroblastic response. Two schools of thought have grown up around this issue: Williams,² Audebert,³ Losee,⁴ and Breitstein¹¹ have been convinced that in those cases where there has been perfect coaptation of the incised tissues, where the various layers have not been separated by blood clot, lochia, or serum, where there has been no infection, the incision heals by complete muscular regeneration in 80 per cent to 90 per cent of the cases. On the contrary, Couvelaire,¹² in 1909, in his report to the Societe d'Obstetrique de France, expressed doubt that the reparative processes could occur without fibrous tissue formation. Fruhinsholz,¹³ Lauvray,¹⁴ and Nicoletti,¹⁵ concurred in this opinion. Schwartz and Paddock¹⁶ appeared to have settled the issue in their exhaustive histological study on "The Cesarean Scar," concluding that muscle regeneration plays no important role in the healing of the scar, and that fibroblastic proliferation was practically normal. In a corroboratory study on a series of uteri from pregnant rabbits they¹⁷ demonstrated the proliferation of fibroblasts along the line of incision entering the interstices between the adjacent muscle bundles. As the scar contracts, this becomes less perceptible, and it is difficult to demonstrate the line of the incision with the ordinary stains after a period of two weeks. It is this marked shrinking of the newly developed connective tissue and its branching penetration among the muscle fasciculae that make the cesarean scar so frequently invisible at a subsequent operation.

spontaneous rupture of the membranes, ran a temperature of 100° to 101° F. for five days following delivery as a result of sapremia. Cystitis was responsible for a temperature of 101° to 102° F. for a two-day interval in two remaining patients. This morbidity incidence is well within the zone of that for the general clinic population, a fact which is deserving of emphasis. When performed in accordance with well-prescribed aseptic technique, manual exploration of the uterus should have no effect upon the morbidity statistics.

The average hospital stay per patient for the group as a whole compared favorably with the general hospital population.

There was one maternal mortality in the series (0.56 per cent) occurring in 1932.

M. M., No. 6414, was a 25-year-old para iii, whose first pregnancy terminated in a normal spontaneous delivery. Two years later a classical hysterotomy was performed in our clinic because of painless, bright vaginal bleeding due to central placenta previa. Convalescence was uneventful. The present prenatal course was normal except for the development of mild pyelitis which cleared readily with conservative therapy, during the seventh month of gestation. Labor commenced spontaneously at term and progressed rapidly under pentobarbital medication. Four hours following admission to the hospital an easy low forceps delivery was performed under N₂O-O₂ ether anesthesia with the birth of a normal, active infant. The uterus was not explored. On recovering from the anesthesia the patient vomited a considerable amount of undigested food. She was well until twelve hours following delivery when she became markedly cyanotic, dyspneic, and apprehensive as a result of a "tightness" in her chest. The pulmonary condition became progressively worse with development of patchy areas of consolidation and bronchial breathing, together with rising pulse and respiratory rate. Exitus occurred forty hours following delivery and was attributed to aspiration pneumonitis. Postmortem examination was refused.

It is difficult to ascribe this disaster to any aspect peculiar to pelvic delivery following cesarean section. Such unfortunate circumstances might have resulted following any operative procedure, and more especially subsequent to a reiterative hysterotomy.

All but six of the infants in this series were discharged in good condition. Two were stillborn with extensive congenital deformities incompatible with life. A third was delivered macerated at thirty weeks' gestation. Another stillborn infant resulted from an easy multiparous breech delivery at term. Intra-uterine asphyxia was attributed to the cord being tightly about the neck twice. A fifth stillbirth resulted at thirty-eight weeks' gestation in a multipara with mild pre-eclampsia who, on admission to the hospital in active labor, was bleeding considerably per vaginam. No fetal heart tones could be heard on admission. Labor progressed rapidly and she was delivered by low forceps at full dilatation of a stillborn 5-pound infant. The placenta showed marked premature separation and infarction. The sixth to be included in the infant mortality was a 7 pound, 15 ounce infant delivered normally at term after a short labor of an RH-negative mother. The infant expired at 24 hours of age of erythroblastosis.

CASE 2.—S. W., No. 3924, 1934, was a 36-year-old gravida vi, para iii, who had had a Kerr hysterotomy in 1928 following a test labor at another hospital. In 1932, a classical section was performed at still another institution. Thereafter, she miscarried three times at ten to sixteen weeks' gestation. When seen in our clinic for the first time she was registered for a third repeat hysterotomy and sterilization one week prior to her estimated date of confinement. Three days prior to the stipulated date of operation she entered the hospital, having been in active labor for four hours. Considerable time was required to locate the patient's spouse, whose signature was necessary for the sterilization procedure. In the one and one-half hours that elapsed the cervix became almost fully dilated and the head low when symptoms of uterine rupture developed acutely. Immediate laparotomy revealed multiple omental adhesions and rupture of the transverse scar with extension into the urinary bladder. The classical scar was found to be intact. Supracervical hysterectomy and reconstruction of the bladder with drainage were performed. The patient was discharged well on the twenty-sixth postoperative day after an afebrile convalescence. The infant succumbed four hours following delivery from atelectasis and intrauterine asphyxia.

CASE 3.—H. B., No. 17503, 1935, was a 30-year-old para iii whose first pregnancy was terminated by forceps delivery, in 1929, with birth of a normal infant weighing 7 lb., 11 ounces. In 1934, she was subjected to a classical hysterotomy for alleged disproportion at another institution. Convalescence was uneventful. While being followed in our clinic, arrangements were made for an elective, repeat section, one week prior to her estimated date of confinement. At thirty-seven and one-half weeks' gestation the patient was suddenly seized with acute abdominal pain and syncope. Laparotomy immediately on arrival at the hospital disclosed numerous adhesions about the old scar and the peritoneal cavity filled with liquid blood and large clots. A one and one-half inch rupture in the uterine scar was extended to permit delivery of a stillborn infant and the placenta which overlay the cicatrix. Scar was excised and uterine incision repaired. Patient was discharged on the seventeenth postoperative day following an afebrile convalescence.

CASE 4.—H. N., No. 13975, 1936, was a 24-year-old para ii whose first pregnancy was terminated by classical hysterotomy for severe pre-eclampsia in our clinic in 1934. She was discharged on the seventeenth day following an afebrile convalescence. Present pregnancy was uneventful until thirty-one weeks' gestation when she developed acute abdominal pain, tenderness over the abdominal scar, with frequency and urgency of urination. Laparotomy revealed complete disruption of the old scar. Nonviable twins and placenta were partially extruded through the rupture. Supracervical hysterectomy with drainage was followed by an afebrile convalescence and discharge on the sixteenth postoperative day.

CASE 5.—M. L., No. 21152, 1937, was a gravida v, para iv, whose second pregnancy was terminated by a Kerr hysterotomy in 1931, and a third pregnancy by classical cesarean section in 1933 because of a suspension and trachelorrhaphy performed one year after her first delivery (pelvic). Both cesareans were performed at another institution. She was registered for a third repeat section and sterilization to be performed one week prior to her estimated date of confinement. On the day prior to the stipulated date of operation, she developed acute abdominal pain. Immediate laparotomy disclosed a dead fetus and placenta free in the general peritoneal cavity, and disruption of the classical scar in its entirety, with extension to involve a portion of the lower transverse

TABLE X. MATERNAL MORTALITY IN UTERINE RUPTURE

AUTHOR	PREVIOUS CESAREANS		NO PREVIOUS CESAREANS	
	CASES NO. OF	MATERNAL MORTALITY	NO. OF CASES	MATERNAL MORTALITY
Findley ²⁷ 1916	59	18 - 30.5%		
Holland ⁵ 1921	97	28 - 28.9%		
Davis ²⁸ 1927	24	3 - 12.5%	82	54 - 65.9%
Sacks ²⁹ 1930			24	14 - 58.3%
Bey ³⁰ 1932			110	56 %
Sheldon ³¹ 1936	7	1 - 14.3%	19	8 - 42.1%
Seley ³² 1937	3	0 - 0 %	9	1 - 11.1%
McNeile ³³ 1938		20 %		90 %
Potters ²³ 1939	51	1 - 2.0%		
Burkous ³⁴ 1941	18	2 - 11.1%	27	15 - 55.6%
B.L.I. cases listed above	8	0 - 0 %		

Barnes (24 weeks),³⁹ Wilson (28 weeks),⁴⁰ Orrul (28 weeks),⁴¹ Nicholson (28, 32, and 34 weeks),⁴² Slevin (30 weeks),⁴³ and Ford (35 weeks).⁴⁴ The accompanying table illustrates that an appreciable number (26.1 per cent) of cesarean scars separate prior to the time when one would ordinarily elect to perform a repeat hysterotomy.

TABLE XI. STAGE OF PREGNANCY AT WHICH RUPTURE OCCURS

AUTHOR	WEEKS												PROPORTION OF CASES OCCURRING AT 38 WEEKS OR EARLIER
	28	29	30	31	32	33	34	35	36	37	38	40	
Findley ²⁷					6				2		3	42	11 - 20.8%
Holland ⁵		1			11		1		14	2	4	53	33 - 37.2%
Singer & Marioton ³⁷					7							14	7 - 33.3%
Mariana ³⁸					7				12		5	111	24 - 17.8%
B.L.I. cases cited				1						1	2	4	4 - 50.0%
Total												224	79 26.1%

In our series of eight cases of ruptured cesarean scars detailed previously, but two such accidents occurred in patients who were selected for prospective delivery through the pelvis. Only one of these patients, however, experienced labor, the second suffering spontaneous rupture before the onset of uterine contractions. The remaining six disruptions occurred without labor prior to the appointed date of repeat hysterotomy, customarily performed one week prior to the expected date of confinement in this clinic. This group of cases reflects in a small way the facts frequently reported in the literature.

We shall not dwell upon the factors that encourage imperfection in the cesarean scar, nor attempt to explain the low incidence of rupture (0.25 per cent) among cervical sections as compared with the frequency (3 per cent to 4 per cent) in the classical type. However, when the uterine incision has been sutured carefully in accordance with well-established surgical principles, and when there has been no subsequent infection as characterized by foul lochia or a febrile convalescence, one may well expect the scar to be capable of withstanding the distention of the maturing pregnancy and the stress of labor itself. With attention directed to the perfect coaptation of the margins of the incision and to the avoidance of muscle infarction, bacterial invasion of the wound will be discouraged. Many have emphasized that placental implantation over the scar

eiatrix. Supravaginal hysterectomy with drainage was followed by an afebrile convalescence and discharge on the seventeenth postoperative day.

CASE 6.—M. B., No. 19663, 1938, was a 25-year-old para ii who in 1936 was subjected to a classical hysterotomy in our clinic because of cephalopelvic disproportion. While being re-examined at thirty-seven and one-half weeks gestation to determine the type of delivery she should have, the patient developed lower abdominal pain and a baseball-sized mass just below the umbilicus. The tumor mass became progressively larger while preparations were being made for operation. Laparotomy revealed rupture of the old scar in its entirety. The membranes were still intact. Following delivery of a living child, supracervical hysterectomy with drainage was performed. The patient was discharged on the nineteenth postoperative day after an uneventful convalescence.

CASE 7.—M. P., No. 19474, 1942, was a gravida iii, paraii, who suffered a fractured pelvis as a result of an automobile accident in 1932. Because of the resultant pelvic deformity an elective classical cesarean section was performed at the Boston Lying-in Hospital in 1936. Convalescence was uneventful and afebrile. The following year she was delivered precipitously of a 6-pound infant at another institution. In this third pregnancy it was elected to permit a test of labor. The patient entered the hospital in mild labor ten days prior to her estimated date of confinement. Following twelve hours of mild labor she suddenly developed severe suprapubic pain. Immediate laparotomy disclosed a dead fetus and placenta free in the general peritoneal cavity, and disruption of the previous classical scar in its entirety. Supracervical hysterectomy was followed by an afebrile convalescence and discharge on the seventeenth postoperative day.

CASE 8.—T. M., No. 38696, 1944, was a gravida ii, para i, whose first pregnancy was terminated by classical cesarean section for placenta previa two years previously at another hospital. X-rays revealed an ample, gynecoid pelvis. It was elected to permit a test of labor. At term the patient suddenly developed severe lower abdominal pain. No labor. On admission to the hospital shortly thereafter immediate laparotomy disclosed a rupture of the previous cesarean scar almost in its entirety. The membranes were still intact, an active infant in good condition was delivered through the rent in the uterus. Supracervical hysterectomy was followed by an afebrile convalescence. Mother and infant were discharged well on the seventeenth postoperative day.

Disruption of cesarean scars forms approximately 20 per cent²⁶ of all uterine ruptures. Though rupture of the uterus is to be considered among the most serious of all obstetric complications, the accompanying statistics disclose that the accident, when a cesarean scar is implicated, is not accompanied by nearly as formidable a maternal mortality as when it results spontaneously or following a traumatic procedure in the uterus free from a cicatrix. The mortality may be conservatively estimated to be in the vicinity of 10 per cent to 15 per cent under the guidance of good obstetric surveillance. The fetal mortality, however, ranges from 70 per cent to 100 per cent.

A sinister feature of rupture of cesarean scars is that the accident may occur at any period of gestation or labor. This adds to the difficulty, however forewarned by our knowledge of the risk to the patient, to protect her completely. Numerous reports of individual cases of spontaneous disruption of the cicatrix in the relatively early stages of gestation have appeared in the literature;

As mentioned earlier, it is our policy in these cases to eliminate the second stage of labor by effecting delivery by low forceps operation at full dilatation of the cervix. We are of the opinion that such conduct is beneficial in avoiding the rigorous stress of the expulsive stage. Intranterine manipulations such as internal podalic version or difficult forceps operations invite traumatic rupture of the uterine scar.

Following delivery, the placenta is permitted to separate spontaneously. Oxytocic preparations are avoided until after the cavity of the uterus has been explored. The administration of pituitary extract usually causes such vigorously sustained contraction of the myometrium that the accoucheur may be unable to insert his hand into the uterine cavity to perform a satisfactory examination, or it may even conceal a small rent in the cicatrix. When the placenta has been expressed, the accoucheur should don fresh sterile gown and gloves, while the perineum is prepared anew and redraped. The entire gloved hand is now placed within the uterine cavity to permit a careful, complete examination. It has been our experience that the greater portion of scars in the lower uterine segment are indistinguishable, whereas a furrow or cleft of varying depth can almost invariably be palpated underlying the classical type of scar. Manual exploration of the uterine cavity should be conducted in a systematic fashion so that small oblique ruptures will not escape detection. All portions of the uterus, including the fundus and the lower segment, must be palpated. The examining fingers are pressed firmly against the inner surface of the uterus by counter-pressure of the external hand, and are guided over all surfaces in four directions: from above, downward; from below, upward; from right to left; and from left to right. It is advisable to repeat the foregoing procedure a second time at the suspected site of the old cesarean scar. Only after the accoucheur has convinced himself beyond any doubt of the integrity of the uterus may both the pituitary and ergot preparations be administered. There is, to be sure, a slight increase in the amount of blood loss associated with delivery as a result of the delayed use of the oxytocic principles.

From an analysis of our own cases and a review of the literature, we cannot but conclude that in properly selected cases that have been previously subjected to cesarean section for some temporary indication, attempts at pelvic delivery are to be encouraged, providing the foregoing precautions are observed. By pursuit of such a policy, one may anticipate not only a considerable curtailment in the frequency of cesarean section, but a gratifying reduction in the maternal mortality and morbidity, as well as a conservation of hospital days.

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predisposes to rupture. It may be this latter factor, together with its site in the noncontractile portion of the uterus, which accounts for the lower incidence of disruptions in cervical scars.

Because of the seriousness of this accident, such pregnancies, labors, and deliveries should be directed by well-trained obstetricians and conducted in maternity hospitals thoroughly equipped to cope with any obstetric complication. The most ideal results are to be expected when the patients are limited to those who have been subjected to a hysterotomy for a temporary indication in one's own clinic, and who are known to have enjoyed an uneventful, afebrile convalescence. As indicated previously, however, we were much more lenient in our selection of cases. The fruitful dividends that eventuate more than compensate the precautions necessary for the successful management of this group of cases.

These patients should be encouraged to seek prenatal care early in their subsequent pregnancies, at which time it is desirable to acquaint them with signs of rupture and to urge them to report promptly any suggestive symptoms. At the initial prenatal visit, or shortly thereafter, the patient's blood type should be determined. Such procedure will conserve valuable time should rupture of the uterine scar occur at any period of gestation, necessitating the prompt administration of blood to combat shock. Hospital blood banks have proved invaluable in just these exigencies.

As suggested by Dippel and Brown,⁴⁵ soft tissue roentgenograms of the anterior uterine wall in the last month of pregnancy might prove useful in determining the relative soundness of the myometrium in the region of a previous longitudinal cesarean wound. We have attempted to visualize the anterior wall thickness in a small series of patients previously delivered by cesarean section and found definite, irregular thinning of the anterior uterine wall in one instance. At the time of repeat hysterotomy, the scar proved to be defective as a result of attenuated fibrous tissue. Only positive findings of this nature would be of value, while negative observations would not preclude the absence of a weak cicatrix.

The patient must be impressed with the significance of entering the hospital at the very onset of labor, rupture of the membranes, or appearance of show. Only by uninterrupted, close observation during labor can the earliest signs and symptoms of impending rupture be detected. A compatible family donor should accompany the patient to the hospital with the intention of remaining in the waiting room throughout her labor and until the successful conclusion of delivery. This precaution must be observed, regardless of the associated inconvenience, unless the institution possesses some other reservoir of blood (blood bank). If labor progresses satisfactorily, one may anticipate a favorable termination, while the intervention of severe uterine inertia may be the factor to influence one to perform a repeat cesarean section. The use of pituitary preparations during such labors is mentioned, only to be unequivocally censured.

THE ARREST OF ABNORMAL UTERINE BLEEDING WITH PITRESSIN TANNATE IN OIL

RALPH C. BENSON, M.D., SAN FRANCISCO, CALIF.

*(From the Departments' Unit of the United States Naval Hospital, Long Beach, California,
and the Department of Obstetrics and Gynecology, University of California
Medical School, San Francisco, California)*

ONE of the most difficult gynecologic accomplishments is the prompt stypsis of uterine bleeding without resort to emergency surgery.^{7, 20} Such bleeding, when prolonged and profuse, hazards the patient's health, efficiency, and comfort. Uterine bleeding is, of course, a symptom and not a disease entity; and accurate diagnosis must always precede final, curative therapeutics. During the period of investigation, however, the quantity of blood lost may be so excessive that a temporary check of the flow may be indicated. Under these circumstances, any simple method which will accomplish this arrest of flow without obscuring subsequent diagnosis or doing harm to the patient is a very worth-while addition to our armamentarium.

The control of uterine bleeding by means of steroid hormones is often contraindicated in premenopausal and adolescent gynecologic patients.^{8, 15, 19, 21} It is also necessary to stop blood loss in other patients in whom the diagnosis has already been established, or in whom so-called "functional uterine bleeding" tends to recur. In short, there are many types of patients in whose treatment we could use a safe, direct, inexpensive uterine hemostatic agent.

Since antiquity, countless medications have been used in the control of menometrorrhagia. Despite this fact we feel that it is appropriate to present our experience with another hemostatic agent in the hope that it may offer advantages over those presently in use.

Pitressin Tannate in Oil offers a new and physiologically sound approach to the prompt arrest of uterine bleeding.

Pitressin—the vasopressor fraction of the posterior pituitary—is a powerful stimulant to uterine contraction in the nonpregnant uterus. In this sense, it offers a mechanical tamponade to uterine bleeding. This is contrary to what we might expect in terms of the reactivity of the parturient uterus. On the other hand, Pitocin—the fraction which is oxytocic in late pregnancy and parturition—is without demonstrable action in the nongravid organ.^{11, 13, 14} The nonpregnant uterus is known to respond clinically to pituitary extract during menstruation.¹⁰ Actually, this oxytocic effect is due to the Pitressin fraction. Such a response is present at every phase of the menstrual cycle, but maximal contraction occurs just before, during, and immediately after menstruation.¹¹

The response of the early pregnant uterus is weak to posterior pituitary fractions. But, the response to Pitressin becomes remarkably strong in incom-

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Results

Table I presents a correlation of the endometrial findings with the clinical diagnoses. Table II presents the results obtained with a single dose of Pitressin Tannate in Oil in the various clinical conditions. Table III presents the results obtained as correlated with the type of endometrium present.

TABLE I. CLINICAL DIAGNOSIS AND ENDOMETRIAL TYPE IN CASES OF ABNORMAL UTERINE BLEEDING TREATED WITH PITRESSIN TANNATE IN OIL.

CLINICAL DIAGNOSIS	ENDOMETRIAL TYPE (BIOPSY)					PER CENT
	ENDOMETRIUM OF PREGNANCY WITH CHORIONIC VILLI	SECRETORY TYPE ENDOMETRIUM	PROLIFERA- TIVE TYPE ENDOMETRIUM	HYPERPLASIA OF ENDOMETRIUM	CASES	
Normal pelvic examination		13	19	6	38	38
Pregnancy complications	7	13	2		22	22
Ovarian failure— natural menopause		1	5	1	7	7
Uterine myomas			6	1	7	7
Salpingitis, acute		3		3	6	6
Ovarian cyst		3	1	1	5	5
Ovarian failure— surgical			4		4	4
Salpingitis, chronic			1	1	2	2
Polyglandular dyserasia			2		2	2
Pulmonary tuberculosis			1		1	1
Pelvic tuberculosis			1		1	1
Hyperthyroidism			1		1	1
Uterine retroversion		1			1	1
Acute respiratory infection			1		1	1
Endometritis (nonpregnant)			1		1	1
Appendicitis, Acute				1	1	1
Total	7	34	45	14	100	100

TABLE II. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL AS RELATED TO CLINICAL DIAGNOSIS

CLINICAL DIAGNOSIS	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	TOTAL CASES	PER CENT
Normal pelvic examination	19	14	5	38	38
Pregnancy complications	6	12	4	22	22
Ovarian failure, natural menopause	4	2	1	7	7
Uterine myomas	3	2	2	7	7
Salpingitis, acute	3	2	1	6	6
Ovarian cyst	2	1	2	5	5
Ovarian failure, surgical	2	2		4	4
Salpingitis, chronic		2		2	2
Polyglandular dyserasia		2		2	2
Pulmonary tuberculosis	1			1	1
Pelvic tuberculosis	1			1	1
Hyperthyroidism	1			1	1
Uterine retroversion			1	1	1
Acute respiratory infection	1			1	1
Endometritis, nonpregnant	1			1	1
Appendicitis, acute	1			1	1
Total and per cent	45	39	16	100	100

plete abortion where the uterus has been sensitized, as it were, for expulsion of the fetus.¹⁴

Moehlig, in 1943,¹² was the first investigator to use pitressin tannate in oil in gynecology. His report, the only one in the literature, describes its use in ten cases. He employed 1 c.c. (5 pressor units) as an initial dose in the control of dysfunctional uterine bleeding. His patients "responded with cessation of flow within six to seventy-two hours following the first or second intramuscular injection of pitressin tannate in oil." Moehlig believed that smaller doses might be effectively hemostatic, but he actually used more than 1 c.c. (5 pressor units) *total* of the drug or more than one injection for the most of his patients.

In a preliminary series of thirteen patients, we administered 1.0 c.c. (5 pressor units) of Pitressin Tannate in Oil intramuscularly. This dose was repeated in forty-eight hours. The results were encouraging, since all patients responded favorably. Seven stopped bleeding completely, and six slackened markedly in forty-eight hours. However, it seemed desirable to eliminate a second injection. We wished to simplify the method and wished to obtain an even better check of bleeding—if this were possible. Therefore, in the series of 100 cases here reported, we administered a *single* dose of 2.0 c.c. (10 pressor units) of Pitressin Tannate in Oil intramuscularly to patients presenting all types of uterine bleeding. No subsequent injections of the drug were employed.

Material and Methods

One hundred consecutive gynecologic patients were treated with Pitressin Tannate in Oil for the control of uterine bleeding. The type of bleeding reported was in all cases prolonged, profuse, or irregular. No screening of patients was permitted in this study—save the elimination of suspected or known pelvic malignancy. Certain patients were pregnant, and abortion was the likely cause of the uterine bleeding. Cases of salpingitis, uterine tumor, ovarian cyst, uterine retroversion, etc., were grouped together. With these we included patients bleeding due to complications of pregnancy and cases of hormone imbalance or dysfunctional uterine bleeding—in order to attack the problem of arrest of uterine bleeding from a wide perspective.

Each patient received a complete physical and gynecologic examination. The blood pressure, pulse rate, and blood-urine findings were recorded. Medical or surgical consultation was obtained prior to gynecologic therapy with pitressin. An endometrial biopsy was secured and Pitressin Tannate in Oil was administered intramuscularly—provided there were no contraindications. The woman was seen again in two days and, when possible, the endometrial biopsy was repeated. A notation of the slackening of bleeding, side-effects, etc., was made. Each patient was required to return for re-examination after the next menstrual period or episode of uterine bleeding.

Many acute gynecologic problems were hospitalized. After ninety-six hours observation for stypsis, all patients received accepted medical or surgical treatment as indicated. In hormone imbalance or deficiency cases, supplementary or regulative endocrine therapy was effected.

Specimens secured at surgery were sectioned and pathologic data added to the facts obtained by the study of the previous endometrial biopsies. A three-month follow-up was attempted in all cases; basal body temperature charts, vaginal smears, and endometrial biopsies facilitated our studies.

TABLE IV. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL IN THE ARREST OF UTERINE BLEEDING AS A COMPLICATION OF PREGNANCY

CLINICAL DIAGNOSIS	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	CASES
Abortion—complete or ? incomplete	4	9	3	16
Postpartum bleeding—after term delivery	1	2		3
Ectopic pregnancy	1		1	2
Pregnancy, early not terminated		1		1
Total	6	12	4	23

TABLE V. CLINICAL DIAGNOSIS AND ENDOMETRIAL TYPE IN CASES FAILING TO RESPOND TO ARREST OF UTERINE BLEEDING WITH PITRESSIN TANNATE IN OIL

CLINICAL DIAGNOSIS	ENDOMETRIAL TYPE (BIOPSY)				CASES
	PREGNANCY ENDOMETRIUM WITH CHORIONIC VILLI	SECRETORY TYPE ENDOMETRIUM	PROLIFERA- TIVE TYPE ENDOMETRIUM	HYPERPLASIA OF ENDOMETRIUM	
Normal pelvic examination		2	2	1	5
Abortion, early	2	1			3
Ovarian cyst		1	1		2
Uterine myomata			1	1	2
Salpingitis, acute		1			1
Ovarian failure—natural menopause			1		1
Uterine retroversion		1			1
Ectopic pregnancy—ruptured		1			1
Total	2	7	5	2	16

to explain these failures, for it is not possible to make any correlation between the type of lesion and lack of effect of the drug. This fact is shown in Table V.

Toxic reactions to Pitressin Tannate in Oil, reported in the literature, include those occasionally noted with aqueous Pitressin:

1. Anaphylaxis
2. Local irritation
3. Intestinal cramps
4. Diarrhea
5. Headache
6. Palpitation
7. Pallor

These signs and symptoms are very rare with the oil preparation. With a long-acting drug of greater effective dosage, however, acute water retention may also be encountered.^{12, 17} The signs and symptoms of this condition include:

1. Rapid weight gain
2. Persistent occipital and frontal headache
3. Listlessness and drowsiness
4. Blurring of vision

Acute water retention may occur in a susceptible individual with as little as 1 unit of pituitrin;¹⁶ but such an occurrence is rare indeed. Alarming cardiac and renal symptoms secondary to vasoconstriction often followed the administration of Pitressin to animal and human subjects during early experimental work with this drug.^{4, 6} However, we now know that the quantity of the drug used was either excessive, or the method of administration abrupt or by non-physiologic routes. The safety of intramuscular administration—even to the hypertensive or cardiac patient—has been established with our lower dosage

TABLE III. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL IN THE ARREST OF UTERINE BLEEDING AS CORRELATED WITH THE TYPE OF ENDOMETRIUM

ENDOMETRIAL TYPE	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	TOTAL CASES AND PER CENT
Secretory	12	15	7	34
Proliferative	25	15	5	45
Hyperplasia	7	5	2	14
Endometrium of pregnancy with chorionic villi	1	4	2	7
Total and per cent	45	39	16	100

Of the 100 patients treated, 31 per cent stopped bleeding in twenty-four hours. Seventeen per cent more stopped bleeding in forty-eight hours. Thirty-nine per cent slackened appreciably with Pitressin Tannate therapy in forty-eight hours or less. Only 16 per cent failed to respond favorably to the drug in the two-day period. Therefore, 84 per cent of all cases of uterine bleeding were benefited to some degree.

The results of Pitressin Tannate therapy were encouraging in cases of:

1. "Functional uterine bleeding" (dysfunctional bleeding).
2. Ovarian failure (natural or post surgical).
3. Menometrorrhagia concomitant with or resulting from constitutional, intercurrent or nongynecologic disease.

Where overwhelming factors causing the uterine bleeding persisted, or where mechanical elements played a part, blood loss continued or was poorly checked. The results of pitressin tannate therapy were discouraging, therefore, in cases of:

1. Retained or adherent placental fragments.
2. Marked pelvic congestion (as with acute salpingitis, etc.)
3. Active or extreme hormone stimulation (haphazard hormone therapy, ovarian tumors or cysts).

It must be stressed that a single injection of Pitressin Tannate in Oil may not completely stop bleeding. Moreover, if bleeding does cease, it may be only for a limited time. Certain cases which showed definite slackening of flow continued to bleed after forty-eight hours and required curettage, abdominal surgery, hormone regulation, etc. This is not a fundamental criticism of the method. Our aim thus far has been to obtain prompt and effective, though admittedly temporary control of uterine bleeding with one injection of pitressin tannate in oil, a long-acting vasopressor-oxytocic preparation. No hemostatic will act indefinitely, and dosage requirements for that purpose are still to be accurately determined.

Curiously enough, one case of threatened abortion was not adversely affected by Pitressin Tannate in Oil therapy plus an endometrial biopsy. The tissue represented decidua only. This procedure followed inaccurate diagnosis on emergency admission. After a check of bleeding, the patient went to term and was delivered of a normal infant. One ectopic pregnancy—a tubal abortion—with a history of prolonged uterine bleeding abruptly ceased to flow following our therapy. The affected tube was removed electively. Generally speaking, however, Pitressin Tannate therapy did not check uterine bleeding adequately where the latter was caused by pregnancy or a complication of the puerperium; nor would the drug seem designed for this purpose. This is evidenced by the results obtained in the treatment of pregnancy complications as presented in Table IV.

Sixteen per cent of the entire 100 patients treated were failures. Bleeding either continued, or, in two instances, was more profuse. We are unable

2. Thirty-one per cent of these patients ceased to bleed in twenty-four hours; 17 per cent more stopped bleeding in forty-eight hours. Thirty-five per cent slackened markedly in forty-eight hours, and only 16 per cent failed to note a check of bleeding. Unfortunately, a comparable control series would be difficult to obtain. It is probable, however, that cessation or slackening of bleeding from simple bed rest, delay, or natural healing processes would not occur so abruptly or in such a high percentage of patients. Moreover, these factors had already been operative in many of the patients of this series without appreciable amelioration of the bleeding.

3. Patients with gynecologic causes for uterine bleeding and those experiencing menometrorrhagia due to intercurrent or constitutional disease responded better to the styptic effect of Pitressin Tannate in Oil than patients with uterine bleeding due to complications of pregnancy—although all groups were benefited.

4. No serious toxic reactions or unusual side effects were noted.

5. Pitressin Tannate in Oil does not appear to alter the endometrial or hormonal pattern in menometrorrhagia. In that sense it is not a cure for the etiologic condition. It is postulated that the action is a mechanical one primarily on the endometrium and myometrium.

Pitressin Tannate in Oil is a water-insoluble preparation of Pitressin suspended in peanut oil. Each cubic centimeter contains sufficient hormone for activity equivalent to 5 pressor units of Pitressin. Supplied in 1-c.c. ampules.

We are indebted to Dr. E. A. Sharp, Director of the Department of Clinical Investigation of Parke, Davis and Company, for the grant of a generous quantity of Pitressin Tannate in Oil for clinical use.

The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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level. There is no evidence that significant cardiovascular symptoms will occur in normal or cardiac patients when pitressin is administered—if it is not given beyond the *cumulative peak dose*. The principal warning of such a dose is abdominal pain and flatulence.⁴ However, good judgment would suggest caution or avoidance of Pitressin therapy in severe nephritic, hypertensive, or cardiac patients. It may be hazardous in those threatened with decompensation or coronary occlusion³ and in the patient with acute thyrotoxicosis.¹⁸

We have cautiously administered Pitressin Tannate in Oil to several patients with moderately severe hypertension, and have not noted any significant rise in blood pressure, headache, precordial pain, etc. Indeed, Pitressin Tannate in Oil has been used in the actual treatment of hypertension.⁵ No patients with serious renal pathology have been treated in this series. In our entire series the reactions were few and mild; they are presented in Table VI.

TABLE VI. REACTIONS TO PITRESSIN TANNATE IN OIL IN THE ARREST OF ABNORMAL UTERINE BLEEDING
(100 Cases Treated)

COMPLAINT	CASES
Headache (frontal and/or occipital)	6
Oliguria (all less than 12 hours)	5
Edema (generalized)	1
Syncope (?—emotional)	1
Total	11

Discussion

With a long-acting preparation like Pitressin Tannate in Oil, there is a continuing release of the active pressor and antidiuretic principles. The usual relaxation of the musculature and vasculature which follows contraction only occurs after considerable time. The effective musculotropic action of Pitressin Tannate in Oil is probably three to six hours; the antidiuretic effect is about twelve to twenty-four hours.⁹ In this series of cases, we have noted a definite, and at times abrupt restraint of bleeding as early as four hours after injection of Pitressin Tannate in Oil. Oliguria may accompany this diminution of bleeding. Within six to eight hours, there is generally more marked stypsis with some continued check of bleeding for forty-eight hours.

Effective contraction of the uterus together with primary vasoconstriction probably allows thrombosis in areas of rhexis, and either cessation or slackening of bleeding occurs. The actual mechanism is of course problematical, but this is a working thesis.

Hemostasis must be attributed to coincidence rather than to drug effect in cases of suppression of uterine bleeding eighteen to twenty-four hours *after* the injection of Pitressin Tannate in Oil. However, in the first twelve hours, once slackening occurs, suppression of bleeding does often continue for forty-eight hours. On the other hand, bleeding may persist if adverse mechanical or hormonal factors are involved.

Conclusions and Summary

1. Pitressin Tannate in Oil (2.0 c.c. or 10 pressor units) intramuscularly was employed as a single injection in 100 unselected gynecologic patients suffering from menometrorrhagia of all types, in an attempt to arrest uterine bleeding. Only cases of pelvic malignancy were excluded.

near future, and thus to salvage more patients suffering from this fell disease. With this initiative, I started the radical vaginal operation in 1932, supplemented by postoperative radiation.

My Plea for Taking Up Radical Vaginal Operation

I believe that I have already made myself clear that, as much as I do not believe in the outstanding supremacy of one particular method of treatment, I do not at the same time deem any particular method as inferior to the other, provided it is efficiently carried out. I have taken up the radical vaginal operation instead of radical abdominal for the following reasons:

1. The primary mortality is much less. Of 151 patients operated upon, six patients died of operation, i.e., a primary mortality of 3.8 per cent as against an average of 14 per cent by the radical abdominal method.

2. Stocky, plump, and adipose patients can be more effectively tackled by the vaginal route.

3. Complications of the nature of ureterovaginal fistulae are much less frequent after vaginal operation than after the abdominal. Even in the hands of some experts, this complication may occur to the extent of 12.3 per cent after the Wertheim operation.

4. The end-results after Wertheim's radical abdominal operation and Schauta's radical vaginal operation are practically the same. In my series, there is 37.6 per cent relative cure rate, as against 39 per cent of Bonney's series.

5. The greatest handicap to the radical vaginal operation is that cancer-affected lymph glands cannot be removed. It has been authoritatively worked out by Bonney, Taussig, and others that there is glandular involvement in from 35 to 40 per cent of all patients presenting themselves for carcinoma of the cervix. Bonney claims that 23 per cent of the cases with gland involvement have passed through a five-year salvage, although the total relative cure rate is 39 per cent. Almost the same relative cure rate has been found in my series of radical vaginal operation without removal of glands. Heyman's series give still better results (absolute cure rate 33.1 per cent) without any surgical removal of glands. Schauta is of the opinion that radical removal of the glands is possibly only in occasional cases; because when the iliac glands, which may be removed, are involved, the aortic group of glands, which are not surgically approachable, are already carcinomatous. Some of the carcinomatous glands are bound to be overlooked because of their small size. Wertheim's opinion is that extirpation of the lymph glands can contribute nothing toward the improvement of end-results. The greater part of the lymphatic vessels infiltrated in a cervical carcinoma run with the uterine veins in the transverse cervical ligaments of Mackenrodt. When these lymphatic channels are infiltrated with carcinoma, cancer cells are well isolated from the rest of the body by the connective tissue sheath of the ligament. The spread of carcinoma is slow in this location because of the marked tissue pressure. Once the cancer cells pass beyond the connective tissue bundle of Mackenrodt, they extend into loose subserous connective tissue: the prospects are no longer good, even if the lesion may be found operable from the technical point of view. But, fortunately, cancer cells remain shut up in Mackenrodt's ligaments for a considerable time and then spread slowly. This slow permeation is the reason why cervical cancer is a relatively favorable type of tumor for operation.

The logical conclusion naturally follows that in operations for cervical carcinoma, the most radical possible excision of the parametrial and paravaginal tissue should be made including also a wide cuff of vagina.

THE EVALUATION OF THE RESULTS OF CARCINOMA OF THE CERVIX UTERI TREATED BY RADICAL VAGINAL OPERATION*

SUBODH MITRA, M.B. (CAL.), M.D. (BERLIN), F.R.C.S. (EDIN.),
F.R.C.O.G., F.N.I.,† CALCUTTA, INDIA

DURING the Third International Radiological Congress in Paris (1931), where I submitted my five-year statistical end-result of carcinoma of the cervix uteri treated with radiation therapy, I was much impressed to find continental surgeons performing the radical vaginal operation in similar cases. On further inquiry, I found that by combining this operation with postoperative radiation, they obtained very satisfactory results. The rationale of the treatment of carcinoma of the cervix is still a controversial subject. Although the general trend of opinion is in favor of radiation therapy, the surgical treatment still occupies a definite place in its management. Moreover, some workers who were previously converts of radiation therapy are coming back to surgery supplemented by radiation therapy.

An analysis of world statistics shows that whatever method be followed (operation or radiation), the end-results are, for all practical purposes, the same in the hands of experts, with a small percentage of variation which may be a chance variation. The popularity of one method over the other depends not only upon the results obtained, but also upon the easy application of the method without harm to the patient. It is the general belief that radiation therapy is much easier to apply. There might be a bit of truth in it, but it is very difficult to check and control whether radiation therapy has been properly executed or not. Experts are of the opinion that "properly performed radium therapy is as difficult to learn as the operation itself." An irresponsible radiotherapist may carry on radiation therapy without being exposed to public criticism because there is much less chance of primary mortality. On the other hand, it has been remarked that the "operation for carcinoma of the cervix as performed by Halban, Adler, or Stoeckel, is much too formidable an operation for general use." My only remark is: does the defect lie in the method itself or in the true make-up of a gynecologic surgeon? Should a gynecologist be worth the name of a surgeon if he considers an important gynecologic operation formidable? I am more than conscious that everybody cannot be a Wertheim, a Bonney, or a Schauta, but can everybody be a Heyman? I believe that it is high time that the fight for the supremacy of one method over the other should come to an end. So far as cancer of the cervix is concerned, a gynecologist who wants to take it up as a life study must be a crack surgeon as well as a first class radiotherapist in order to work out by the process of evolution a more suitable technique in the

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†Professor of Obstetrics and Gynecology, Carmichael Medical College; Director, C.S.S. Cancer Hospital, Calcutta, India.

scissors, and not merely pushed laterally without making any clear-cut demonstration of its topographical anatomy. Occasionally, the inferior vesical artery and vein may be cut during the process of dissection and should be ligatured.

After the vesical pillar has been further dissected up and laterally, the uterine vessels will be found near the junction of the cervix with the body of the uterus. As the uterine bundles are dissected and followed up laterally up to 1 to 2 centimeters, the deeper part of the ureter and its bend will be visible. This bend becomes more acute by pulling the uterus down.

When there is infiltration of the parametrial tissue the ureter is drawn closer to the uterus, and becomes adherent to its lateral aspect, and thus is apt to be injured even before the uterine bundle is made properly visible. It would be advisable for the beginner to cut through only those tissues which can be distinctly differentiated, and, as soon as the thicker strand of tissue is found extending from above downward, care must be taken of the ureter and an endeavor made to separate it from the uterine bundle, which courses rather transversely, by means of a closed pair of scissors. It is dangerous to make a blunt dissection with gauze, because if so, uterine bundles may be partly torn and the topographic representation will be altered. The ureter thus freed will appear as a typical whitish structure sometimes showing peristaltic contractions. The future dissection of the ureter and its separation from the uterine bundle will not be difficult.

The Radical Removal of the Parametrial Connective Tissue Is the Important Step of the Operation.—Extensive dissection and the steps of the operation so far followed are meant only to facilitate the radical removal of pelvic connective tissue. By opening the uterovesical pouch, the uterus is brought forward and separated with the appendages. The uterus now remains attached by the parametrial and paravaginal tissue, as well as by the uterosacral ligaments. First the rectum should be definitely separated from the uterosacral ligaments. To make the operation radical, it would be better to pull down the fundus by a strong pair of vulsellum forceps and the cervix by means of the traction thread on the right side, thus making the whole of the left parametrial tissue quite taut, and then divide with a pair of sharp scissors in one sweep as far laterally as possible, avoiding the rectum below and the ureter above. There might be a spurting middle hemorrhoidal artery or its branch which is easily ligatured. The amount of parametrial tissue removed on each side is to the extent of about two and one-half inches.

Postoperative Complications

Six patients died, the primary mortality being 3.8 per cent; three patients died of shock, one of pulmonary embolism on the fourteenth day, one of pneumonia, and one of staphylococcus septicemia.

The bladder was injured in six patients, of whom two required an operation for perfect recovery, whereas fistulae healed spontaneously in four other cases. In one case the ureteric wall was so much thinned out during dissection that it was almost on the point of rupturing, but by careful stitching of the outer coat nothing untoward happened. In three cases there was injury to the rectal wall, due to Schuehardt's incision, but it healed spontaneously. In 23 per cent of the patients the perineal incision did not unite by first intention, but later on healed by granulation. *Bacillus coli* infection is a common factor during the postoperative period to the extent of about 54 per cent. In four of my cases pyometra was present.

The abdominal route was preferred originally because great hopes were placed in the removal of the glands: the excision of parametrial tissue was never considered as important as the removal of lymphatic glands.

6. The percentage of recurrence does not differ greatly after the two methods of operation, abdominal or vaginal. Kamnicker, after making an extensive analysis of the materials of the first and second Universitäts Frauen Klinik in Vienna, has found 55 per cent local and 30 per cent glandular recurrences in Schauta's operation, against 69 per cent local and 26 per cent glandular in Wertheim's operation.

7. The surgeon, expert in vaginal technique and thoroughly conversant with the surgical anatomy of the pelvis, can remove a greater amount of parametrial, paravaginal, paravesical, and pararectal connective tissue by the vaginal route with Schuchardt's incision than by the abdominal route. In my series, parametrium has been removed to the extent of about two and one-half inches from each side.

8. Lastly, the radical vaginal operation facilitates the introduction of radium in the parametrial tissue immediately or shortly after operation.

Technique (Special Points)

The carcinomatous growth is cauterized with surgical diathermy on the day previous to operation and dusted with "Cibazol" powder. Adrenalin (0.5 c.c.) with normal saline (70 to 100 c.c.) is next injected to the left side of perineum near the site of Schuchardt's incision.

Vaginal Cuff.—I make the vaginal cuff first when the vaginal outlet is very relaxed and the pelvis is one of gynecoid type, because by the time the cuff is made, adrenalin, already injected in the perineal tissue, will have its full effect. But if the vagina is narrow or the pelvis is one of anthropoid or android type, or if the growth is still a big one after cauterization, I make a Schuchardt's incision first. The making of the vaginal cuff is one of the most important steps of the operation. It is meant not only to cover the growth of the cervix, but to excise along with it quite a large amount of vagina and paravaginal connective tissue proportionate to the extent of the growth. The disadvantage is that the vagina becomes very small in some cases and inconveniences marital life, but recurrence of growth mostly occurs in the vaginal scar if sufficient vagina is not removed.

Schuchardt's Incision (Vagino-perineo-levator incision).—This incision is generally made on the left side and it is better not to make the incision in one sweep, but in different layers. When the incision is properly made and a broad speculum inserted posteriorly, the approach to the internal genital organs with their attachments will be quite easy. The bladder and rectum are freely dissected out. Generally, this dissection is quite easy, but the difficulty arises as a result of any prior operation scar or too much scar tissue formation resulting from previous radium treatment, or due to marked infiltration of the base of the bladder extending from the cervix. Sometimes difficulties can be overcome by trying to free the bladder from the side instead of in the middle line. The bladder should be mobilized freely, not only in the middle line but also from the sides, and pushed beyond the uterovesical ligaments.

When the bladder has been freely dissected up to the uterovesical pouch and the uterovesical ligaments have been clearly exposed, the important stage of the operation, viz., the dissection of the uterine artery and ureter, begins. The ureter should be dissected freely and displaced laterally and upwards in order to make possible the removal of the maximal amount of the parametrial tissue. The dissection should be made by small steady and careful cuts with a pair of

lous precision. It is only by the detection of early cases and centralization of patients in special cancer clinics that we can markedly improve our end-results and hence the right movement should be the education of lay public and special courses of cancer training for the general medical practitioners. I would like to quote a few lines from Bonney which I presume bespeaks the sincere aspiration of every gynecological surgeon: "So far as operation is concerned, apart from its effect on carcinoma of the cervix, it has been and still is a great educational factor in gynecology, and it has raised the reputation of gynecologic surgeons in the opinion of surgeons in general, for the procedure is the most difficult of all surgical procedures. It has taught us the anatomy of the pelvis in a way that no dissecting room preparations could possibly have taught, and it has enlarged the surgeon's vision, so that, though in the future we may quite possibly see it replaced by a treatment more efficient, its disappearance from the field of gynecology will not be an entire gain."

Statistical Analysis

For proper assaying of statistical results three things are essential, viz., operability rate, relative cure rate, and absolute cure rate. For the last twenty years I have been classifying my cases according to the League of Nations' formula and, since 1932, operation has been undertaken as a side chain to radiotherapy. Materials for operation were taken not only from Grades 1 and 2, but also from Grade 3. Thus, 42.6 per cent of Grade 1, 28 per cent of Grade 2, and 5 per cent of Grade 3 cases were operated upon, and the rest were treated with radiation therapy. Although all the clinical material was at my command, I did not insist on operation for all cases which were deemed operable. Patients were given a free choice, and operation was done only to willing patients, although I have found by careful scrutiny that 57.7 per cent of all cases could have been operated. I have operated on 151 patients, six of whom died of operation, the primary mortality being 3.8 per cent. The total number of patients operated upon between 1932 and 1940 is ninety-three. Five-year salvage cases totalled 35, i.e., a relative five-year cure rate of 37.6 per cent. The total number of patients operated upon between 1937 and 1940 is 40, of whom 16 patients were well after five years, thus yielding a relative five-year cure rate at 40 per cent. The total number of patients operated upon during 1932 to 1936 is 53, of which 19 were well after five years, and 13 after ten years, thus giving a relative cure rate of 36 and 24.5 per cent, respectively. When taken separately in different Grades, the five-year relative cure rates were 61.5 per cent of Grade 1, 44 per cent of Grade 2, and 15.6 per cent of Grade 3.

Against these figures and during the same period between 1932 and 1940, my five-year relative cure figures by radiotherapy are 66 per cent in Grade 1, 31.5 per cent in Grade 2, 12.6 per cent in Grade 3, and 2.3 per cent in Grade 4.

Unfortunately, I cannot give an absolute cure rate of my cases from 1932, as the patients cannot be grouped under one particular method of treatment. Result will certainly be vitiated if an attempt be made to find out an absolute cure rate of operation cases against the bulk of remaining cases who were treated by radiotherapy.

My results from radiation therapy from 1926 to 1932 are as follows: the relative five-year cure rates are a 53.4 per cent of Grade 1, 37.5 per cent of Grade 2, 9.4 per cent of Grade 3, 1.7 per cent of Grade 4. The absolute cure rate is at 12.9 per cent after five years and 9.4 per cent after ten years.

It is evident that the results of radiation are not so striking as those of operation. So far as radiation therapy is concerned, I am afraid my technique is perhaps not very accurate and precise. Besides, my hospital cannot afford to give free treatment to all patients, thereby sustaining a loss of the early cases. The patients are mostly poor and irresponsible. A good number of them (18.3 per cent) did not take the complete course of treatment, either because they could not afford it, or they thought they were cured in spite of repeated insistence to the contrary. Moreover, there being no arrangement for registration system, patients once changing their residence could hardly be traced. Lastly war, famine, flood, and communal disturbances have practically dislocated the civil life, thereby making difficult the following-up system. If I take a relative cure-rate of only those cases who have taken a complete course of treatment, the results will be 14.9 per cent, which stands comparable with the results of other workers.

Conclusions

In conclusion, I must admit that we have as yet no remedy for advanced cases. Operable cases yield satisfactory results up to a certain limit whatever method is followed, provided treatment be given efficiently and with meticu-

On readmission to the hospital, however, on Nov. 5, her general condition had definitely deteriorated and there was marked swelling of the right leg. Cystoscopic examination showed no bladder involvement, but vaginal examination showed a sloughing area deep in the posterior lip of the cervix extending back to the rectum. Therefore, the insertion of radium was abandoned. Subsequent to leaving the hospital the patient had two moderate vaginal hemorrhages and died after about six weeks. It is well known that the prognosis in carcinoma depends on the absence or presence of glandular involvement, and it seems unlikely that this patient was fortunate in this respect, even when first seen.

The second case occurred in the same hospital in 1931, and concerns a white woman, aged 47 years, gravida viii. She had had some prolapse for thirteen years following her last delivery, and procidentia for two years. The cervix showed an ulceration from which the biopsy was diagnosed, "squamous cell carcinoma," 4,800 mg. hours of radium were used, and three months later a vaginal hysterectomy was done. Seven years later the patient returned because of a recurrence in the vaginal vault for which she was given more radium. She is still attending the Follow-up Clinic.

These two cases of carcinomas of the cervix, complicating procidentia, were the only ones found in the years between 1931 and 1946 in the records of the Woman's Medical College Hospital, although during these same years there were 274 admissions for carcinomas of the cervix. At The Woman's Hospital of Philadelphia there were no cases of the type we are considering and 132 cases of cervical malignancy during the same years.

In reviewing the literature on this subject of carcinoma of the prolapsed cervix, the matter of incidence is very striking. It has been estimated in the United States yearly for the past twenty-five years that approximately 26,000 women have died of cancer of the uterus, over 80 per cent of them of cancer of the cervix. It has also been estimated that 4 per cent of erosions of the cervix develop carcinoma, first the one and then the other being based upon chronic irritation.

What are the statistics of cancer with procidentia where the cervix is especially subject to such irritation? In 1935, Brady summarized the literature, and I use this summary in several of the following references. In 1882 Fritsch said that the two conditions did not occur together. In 1893 Pontow collected 29 cases. Cullen at Johns Hopkins saw only one case, and Martzloff of the same institution reported in 1923 no cases to be found in that Hospital's statistics. Haegler at the second Frauenklinik in Vienna found five cases in 11,045 women, at the same time reporting the incidence of cancer of the cervix in women without procidentia as 7.2 per cent.

In 1930 a questionnaire sent to leading American gynecologists revealed the fact that 52.3 per cent had never seen a case, and another 27 per cent had seen only one. In 1931, Delvaux wrote to Hartman of Paris, Schroeder of Kiel, and Sellheim of Leipzig. These eminent gynecologists had seen no such cases. Smith, Graves, and Pemberton, after careful microscopic study, found one case in 683 prolapsed uteri. On the other hand, Emmert and Táussig in 1934 reported four cases observed in ten cases of procidentia. By 1943, seventy-eight cases were collected from the literature.

What explanation can be given by those who consider it a rare combination, as to the cause of its rarity? As Graves said, "It seems remarkable that the prolapsed uterus seems almost immune to cancer, despite the irritation, hypertrophy, impaired circulation, and infection which predisposes to squamous cell cancer in the normally located cervix." The chief theory advanced is that cornification of the epithelium in prolapse raises the resistance to cancer.

CARCINOMA OF THE CERVIX COMPLICATING PROCIDENTIA UTERI*

DOROTHY L. ASHTON, M.D., PHILADELPHIA, PA.

THE following case is presented primarily as an addition to the rather small number of reported carcinomas of the prolapsed cervix. It may also be looked upon as one embodying a series of frustrations for the physician not unusual in the age group in which this disease most frequently occurs.

It concerns M. S., a white widow, aged 74 years. She was admitted to The Woman's Medical College Hospital of Pennsylvania on Aug. 10, 1946, with the chief complaint of "something coming down." Although she had had a sense of bearing down for thirty-one years since the birth of the last of her six children, she did not notice an actual protrusion until four years ago. For ten months the uterus had been prolapsed at all times and was not replaceable. During this time the patient had almost no control of her bladder and there was a malodorous discharge, often bloody. She had lost forty pounds in the past year. Her menopause occurred at 48 years and was uneventful. She had been generally well, except for her chief complaint and gall-bladder trouble for the past two years.

On physical examination the positive findings included malnutrition, avitaminosis, a systolic murmur over the precordium, blood pressure 95/60, and varices of both legs, especially the right. The white cell count was 14,600. A uterus the size of a small orange protruded through the vaginal orifice, and on the lower portion of this there was a fungating, friable, bleeding, irregular, red, foul-smelling mass twice the size of the uterus. The vaginal walls were leathery and the bladder fold not distinguishable. A biopsy of the cervix taken on August 12, revealed "an infiltrating, malignant tumor arising from stratified, squamous epithelium, with surface ulceration and hemorrhage." As many as seven mitotic figures could be identified in the high-power field. The pathologist's impression was grade 3 carcinoma of the cervix. Roentgen examination showed no evidence of metastases to lungs, thoracic cage, or shoulder girdle.

The treatment proposed consisted of x-ray, radium, and operation if indicated, in this order. Accordingly x-ray treatments were instituted and a total dosage of approximately 4,000 R.U. was given to the tumor. After this the patient developed ulcerations as large as the palm of the hand on the inner side of each thigh, probably due to an erythema, bathed in urine and discharge from the tumor. She was sent home, therefore, to return later for radium insertion.

She was readmitted, however, in a week for acute abdominal pain and jaundice. X-ray showed many small stones in the gall-bladder but no liver enlargement or evidence of skeletal metastases. After recovery from this attack she was again discharged. In four weeks the uterus was small enough to be replaced with difficulty, and a Menge pessary was inserted and left in for ten days. This was done in order that the patient could be out of bed (she had been unable to sit up while the mass protruded), that urinary leakage could be controlled, that the thigh ulcers could heal, that the uterus could be relieved of congestion, and that the general physical and mental condition could be improved.

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the August, 1934, issue of *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*.¹⁷ The second patient was treated at Jefferson Hospital in 1942 because of a group 2 Schmitz' carcinoma. There was a third degree cystocele and a rectocele. The patient was treated with deep x-ray therapy, and a few months later received local radium to a total of 4,400 mg./hr. It was interesting in going over the notes that in December, 1942, after radium had been given in July, that the prolapse was no longer apparent. In November of this year there was no prolapse present, but there was a small symptomless cystocele. The patient described herself as well in every respect.

Two additional cases were noted at Jefferson. One was a patient of Dr. David Farrell, a group 1 lesion. She was treated with deep x-ray therapy followed by radium. The patient had a cystocele with procidentia and a third degree rectocele. This case was treated two and one-half years ago, and at the present time there is no prolapse and no apparent rectocele and a small cystocele. Her only complaint is occasional stress incontinence. This patient was not told of her malignancy, but thinks that the local radium and x-ray were given to cure her prolapse. Dr. Scheffey has asked me to present a case which he treated three years ago for procidentia with carcinoma of the cervix. The patient was given deep x-ray therapy and radium with regression of the prolapse. Dr. Scheffey felt this might be a patient suitable for Meigs-Wertheim type of radical complete hysterectomy. However, it was impossible to isolate adequately the ureters. In fact, dissection throughout was extremely difficult. The usual complete hysterectomy was done, and the patient returned to her room. Her convalescence was complicated by an unusual amount of sloughing in the vaginal vault. One year later the patient felt well, but there was still an ulcer $1\frac{1}{2}$ cm. in diameter in the vault.

Dr. Ashton has mentioned the theories in regard to the rarity of procidentia associated with carcinoma of the cervix, and the need for the further study of cervical decubitus ulcers to see if the rarity is real or apparent. I would like to emphasize irradiation in the treatment of cervical cancer, whether associated with procidentia or not. After having reviewed these cases I was quite struck with the results of x-ray therapy in the correction of the associated prolapse, and I might even recommend that it be used electively to treat prolapse of the uterus.

In answer to Dr. Philip F. Williams' question concerning the ages of the patients: Dr. Farrell's case was 54 years of age. The first ward case at Jefferson was 56 years of age. The second ward case was 66 years, and the private case of Dr. Scheffey's was 68 years.

Emmert and Taussig challenge this by reference to the frequency of cancer of the lower lip of the face, and to their series of four carcinomas in ten cases of procidentia. They claim that "because it occurs in elderly women (50 per cent are over 60 years of age), in atrophic tissues, and where lymphatics are stretched and somewhat occluded, it is not very active;" and insist that more cases would be found if more decubitus ulcers were sectioned. One might answer by referring to the usual rapid healing of such ulcers before operation is undertaken, which healing in itself rules out malignancy. The question remains for future settlement.

As to treatment, although there is great temptation to do an early vaginal hysterectomy, this is not at present the accepted treatment, except in very early cases, any more than it is the accepted treatment of cervical cancer inside the vagina. Because of the presence of infection x-ray should be used first. This gives a uniform distribution of radiation, combats infection, and shrinks the tumor. Radium can then properly be used after replacement of the uterus, without the danger of severe pelvic infection and septicemia. It is interesting to note that subsequent operation is frequently unnecessary, although the exact mechanism by which the procidentia is relieved or cured is not known, unless it can be explained by the shrinkage of the supporting structures and reduction of the volume of the uterus.

In conclusion, it may be reiterated that the chief interest in this subject of carcinoma of the completely prolapsed cervix lies in its seeming rarity, and suggests the need for more detailed study of decubitus ulcers to prove whether or not that rarity is real. Certainly the preponderance of evidence points to a true scarcity, and arouses interest in an adequate explanation of such an arresting apparent paradox.

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1930 CHESTNUT STREET.

Discussion

DR. GEORGE A. HAHN.—At the Oncologic Hospital since 1929 we have had about three hundred cases of carcinoma of the cervix, but no cases associated with procidentia. There was one patient who had been treated elsewhere; she had a Watkin's interposition performed because of moderate pelvic relaxation without complete prolapse, and at biopsy carcinoma of the cervix was found. She has since been treated and has remained well for four years. At Jefferson about 600 patients with primary carcinoma of the cervix have been treated on the ward service since 1920, and of that number there have been two cases with associated procidentia. The first of these patients was seen in January, 1933, with a prolapse of nineteen years' duration. Because of edema and the extent of the carcinoma the prolapsed organ could not be replaced within the vaginal orifice. X-ray treatment was given and the uterus regressed within the introitus. However, the carcinoma continued to advance and the patient died two months later. This case was reported by Dr. Scheffey in

diagnosis in one case was changed to carcinoma and four others were interpreted as suspicious. The remaining fourteen were still considered to be negative. The reasons for failure of the biopsy method are three. First, the majority occur because the surgeon did not choose the right area to biopsy. Some early cancers are grossly undetectable, and even with Schiller's iodine and the colposcope it may be impossible to locate the region involved in such tumors. Second, there are occasional errors due to misinterpretation of the specimen submitted. However, it is important to point out that the recognition of early structural changes pathognomonic of preinvasive cancer are recognized more often at the present time than they have been in the past. Smith and Pember-ton,¹⁰ Taylor,¹¹ and others, on reviewing cervical biopsies taken from three to eight years before, have found a number in which they have felt justified in reversing a previous negative report. Lesions now diagnosed unquestionably malignant may have been previously called benign. The third reason for errors in the biopsy method is that occasionally tissue must be considered "insufficient" for diagnosis. This usually occurs when no cervical epithelium is included on the slide. A cervical biopsy is at best a small piece of tissue which after fixation is difficult to orient in the paraffin block. Unless sections are made at right angles to the surface, all the epithelium may be shaved off and discarded with the initial segments of the paraffin ribbon. Davis,¹² in 1932, reported that 25 per cent of cervical biopsies failed to show any epithelium, and thus had to be reported as inadequate.

Of the 181 cases of epidermoid carcinoma, there were seventeen, or 9.4 per cent, in which the first vaginal smear was reported negative (Table I). These "negative" smears were reviewed carefully, and eight showed cancer cells on review. The reasons for failure in the vaginal smear method are three. Occasionally a tumor will not desquamate cells into the vagina. In this instance a negative diagnosis will be made although the patient may have uterine cancer. Second, cancer cells may have been present on the slide but not seen at the first examination. Every field of the slide must be covered or in certain cases malignant cells will be missed. Third, malignant cells may be misinterpreted as benign. It is obvious that an error of this kind will occur in any new method, but with more knowledge concerning the individual characteristics of malignant cells there should be a reduction in these mistakes.

TABLE I. PRIMARY EPIDERMOID CARCINOMA OF CERVIX. 181 CASES

	FIRST SMEAR REPORT	FIRST BIOPSY REPORT	TOTAL	
			NUMBER	PER CENT
Both methods right	+	+	148	81.7
False negative biopsy	+	-	16	8.8
False negative smear	-	+	14	7.7
Both methods wrong	-	-	3	1.7
			181	100

It is important to point out that although the first biopsy report was negative in 10 per cent of the cases and the first vaginal smear report negative in 9 per cent, there was only a 1.7 per cent error in initial diagnosis when the results of both methods were combined. This indicates that each method is complementary to the other. One should not be used to the exclusion of the other; together, they serve as checks upon one another. Whereas the biopsy makes the excised tissue alone available for study, the vaginal discharge contains examples of cells cast off from the whole of the epithelium of the cervix and uterus. This particular attribute of the vaginal smear suggests that it is of special value in those cases where the cancer is small or hidden from view

A COMPARISON OF THE ACCURACY IN DIAGNOSIS OF THE VAGINAL SMEAR AND THE BIOPSY IN CARCINOMA OF THE CERVIX

RUTH M. GRAHAM, B.S., SOMERS H. STURGIS, M.D., AND
JOHN MCGRAW, M.D., BOSTON, MASS.

(From the Vincent Memorial Laboratory of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital)

UNTIL recently the only accepted procedure in establishing a diagnosis of cervical malignancy was by the standard biopsy technique. However, the demonstration by Papanicolaou¹ in 1941 that uterine carcinomas cast off cells into the vagina which could be recognized as malignant in a high percentage of cases introduced a cytologic method of diagnosis as a supplement to the histologic examination. In 1943 Meigs et al² confirmed the diagnostic accuracy of the vaginal smear, and since that time many reports³⁻⁷ have emphasized both the value and accuracy of the cytologic approach to the diagnosis of uterine cancer.

During the past four years over 5,000 vaginal smears from 3,800 cases have been examined at the Vincent Memorial Laboratory. The diagnoses obtained by these smears in relation to the final histologic reports have been analyzed elsewhere.^{2, 8, 9} It is the intention of this paper to examine the accuracy of the cytologic and histologic methods by a comparison of the initial vaginal smear and the initial cervical biopsy in proved cases of cancer of the cervix. An attempt has been made to analyze the reasons for failures in both methods.

Material

It was felt that a fair evaluation of the biopsy and vaginal smear methods could be obtained by limiting the cases studied to those with primary epidermoid carcinoma of the cervix. In any series of uterine malignancies the surgeon should have the best chance in this group of recognizing and sampling the areas under suspicion. Only cases that had both biopsy and vaginal smear before radiation have been included. Only those in which both the biopsy specimen and the vaginal smear were available for review were used. Since 1942, when the Vincent Memorial Laboratory started to examine vaginal smears, until Dec. 31, 1946, there have been 228 epidermoid cervical carcinomas studied by this method. Forty-seven of these were omitted from this group because they were recurrent cases, had had previous radiation, or the biopsy specimen was taken at another hospital and was not available. There were, therefore, 181 cases that could be included in this study group.

Results

In 148 of these 181 cases, or 82 per cent, both the first vaginal smear and the first cervical biopsy were positive for cancer. There were sixteen false negative biopsies and fourteen false negative smears: in addition to these there were three cases in which both methods failed.

There were in all 19 cases, or 10.5 per cent, in which the first biopsy was negative. These errors in the biopsy method were carefully reviewed. The

TABLE IV. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX, 19 CASES IN WHICH THE FIRST PATHOLOGIC REPORT WAS NEGATIVE FOR MALIGNANCY*

NUMBER	SMEAR DATE AND REPORT	INITIAL STAGE	PATHOLOGY			PATHOLOGY REVIEWED
			DATE	OPERATION	REPORT	
TC 229	5/5/44 negative	I	5/ 2/42 3/ 8/44	Biopsy Hysterectomy	Acute inflamma- tion Epidermoid Ca Grade III	Suspicious
M 149	1/18/43 positive	0	12/ 4/42 1/ 3/43	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Negative
M 116	11/18/43 positive	I	11/18/43 12/ 8/43	Biopsy Biopsy	Cervical polyp Epidermoid Ca Grade III	Negative
TC 61	2/4/43 positive	II	1/27/43 2/18/43	Biopsy Hysterectomy	Leukoplakia Epidermoid Ca Grade I	Atypical leukoplakia
TC 417	4/29/44 positive	I	4/29/44 5/13/44	Biopsy Hysterectomy	Acute and chronic inflam- mation Epidermoid Ca Grade III	Negative
TC 440	5/6/44 positive	I	5/ 6/44 5/19/44	Biopsy Hysterectomy	Acute inflamma- tion Epidermoid Ca Grade I	Negative
M 414	6/23/44 negative	0	7/15/44 7/17/44	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Negative
TC 614	8/5/44 negative	0	8/ 7/44 8/12/44	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Negative
TC II94	6/30/45 positive	I	7/14/45 7/27/45	Biopsy Hysterectomy	Chronic cervicitis Epidermoid Ca Grade III	Negative
TC 1294	9/4/45 positive	0	8/31/45 9/ 7/45	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Suspicious
TC 311	11/17/45 positive	I	8/ 7/45 9/21/46	Biopsy Hysterectomy	Chronic cervicitis Epidermoid Ca	Suspicious
M 1054	1/23/46 positive	0	1/30/46 2/13/46	Biopsy Cervicectomy	Inadequate Cancer in situ	Negative
TC 1636	2/12/46 positive	II	2/12/46 2/15/46	Biopsy Hysterectomy	Chronic cervici- tis, sev. Epidermoid Ca	Epidermoid Ca
M 1093	2/13/46 positive	0	2/13/46 3/ 6/46	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Negative
TC 1766	3/30/46 suspicious	II	3/30/46 4/ 6/46	Biopsy Biopsy	Acanthosis Epidermoid Ca Grade III	Suspicious
TC 2032	4/5/46 positive	IV	7/20/46 7/27/46	Biopsy Biopsy	Probable Ca Necrosis	Necrosis—no cellular de- tails
TC 2219	7/20/46 positive	I	10/19/46 11/2/46	Biopsy Biopsy	Chronic cervicitis with squamous metaplasia Epidermoid Ca Grade I	Negative
TC 2331	11/27/46 positive	0	12/10/46 2/ 4/47	Biopsy Hysterectomy	Chronic cervicitis Cancer in situ	Negative
TC 2381	12/10/46 positive	0	12/14/46 3/14/47	Biopsy Hysterectomy	Leukoplakia Cancer in situ	Negative

*Includes the three cases in which the first vaginal smear was also negative for cancer.

TABLE II. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX
INITIAL STAGE OF THE DISEASE MISSED BY FIRST DIAGNOSTIC TEST*

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV
17 Negative smears	2	6	4	4	1
19 Negative pathologic reports	8	7	3	0	1

*The three cases initially missed by both smear and pathology are included in both the negative smear and pathology groups in this chart.

TABLE III. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX, 17 CASES IN WHICH THE FIRST VAGINAL SMEAR WAS NEGATIVE*

NUMBER	SMEAR DATE AND REPORT	INITIAL STAGE	PATHOLOGY			SMEAR REVIEWED
			DATE	OPERATION	REPORT	
TC	7/10/43	II	7/10/43	Biopsy	Epidermoid Ca	No Ca found
187	negative					
TC	1/31/44	I	1/15/44	Biopsy	Epidermoid Ca	No Ca found
262	negative					
TC	5/5/44	I	5/ 2/42	Biopsy	Acute inflamma- tion	Mistake; Ca present
229			3/ 8/44	Hysterectomy	Epidermoid Ca Grade III	
M	6/23/44	0	7/15/44	Biopsy	Chronic cervicitis	Mistake; Ca present
414	negative		7/17/44	Hysterectomy	Ca in situ	
TC	8/5/44	0	8/ 7/44	Biopsy	Chronic cervicitis	No Ca found
614	negative		8/12/44	Hysterectomy	Ca in situ	
TC	3/15/45	I	3/18/45	Biopsy	Epidermoid Ca	Mistake; Ca present
984	negative				Grade II	
M	8/2/45	II	8/13/45	Biopsy	Epidermoid Ca	Mistake; Ca present
733	negative				Grade II	
M	8/29/45	III	8/29/45	Biopsy	Epidermoid Ca	No Ca found
875	negative				Grade II	
M	9/17/45	I	9/17/45	Biopsy	Epidermoid Ca	Mistake; Ca found
885	negative				Grade III	
TC	10/20/45	I	10/20/45	Biopsy	Epidermoid Ca	No Ca found
1387	negative				Grade III	
TC	11/19/45	IV	11/19/45	Biopsy	Epidermoid Ca	No Ca found
1452	negative				Grade III	
TC	1/4/46	III	1/ 7/46	Hysterectomy	Epidermoid Ca	Mistake; Ca present
1532	negative				Grade III	
TC	4/1/46	II	4/ 4/46	Biopsy	Epidermoid Ca	Mistake; Ca present
1774	negative				Grade III	
M	4/1/46	I	4/16/46	Cervicectomy	Early invasive Epidermoid Ca	No Ca found
1197	negative					
M	5/13/46	II	5/13/46	Biopsy	Epidermoid Ca	Mistake; Ca present
1291	negative				Grade III	
TC	6/26/46	III	6/27/46	Biopsy	Epidermoid Ca	No Ca found
1993	negative				Grade III	
TC	II/6/46	III	11/ 6/46	Biopsy	Epidermoid Ca	No Ca found
2269	negative				Grade II	

*Includes the three cases in which the first biopsy was also negative for cancer.

within the external os, the very cases that give the surgeon little indication of likely areas to biopsy, and thus the particular ones in which the biopsy is most likely not to include malignant tissue. On the other hand, in those cases in which cancer cells fail to desquamate into the vagina and therefore the vaginal smear is negative, the biopsy may often give a positive diagnosis.

It is of particular importance to note which method proved to be the more reliable in diagnosing early lesions. According to the League of Nations Classification, Stage I applies to an early cancer completely confined to the cervix. We have further differentiated this group by classifying the preinvasive type of cancer (carcinoma-in-situ) as Stage 0. Chart II compares the

PREGNANCY FOLLOWING TUBAL STERILIZATION

WM. J. DIECKMANN, M.D., AND ELIZABETH B. HAUSER, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, University of Chicago and
The Chicago Lying-in Hospital)*

PREGNANCY has occurred after hysterectomy and after bilateral salpingo-oophorectomy. The only certain method of preventing conception is the complete removal of ovaries, tubes, and uteruses. This operation is castration, but to the laity it is synonymous with sterilization. The latter term may also mean castration, but to the physician it signifies some procedure designed to prevent conception without interfering with ovarian function. The simplest method for preventing conception is to block the lumen of the Fallopian tubes. However the large number of operations on the tubes designed to prevent pregnancy indicate that the number of failures is large.

Eastman, in 1936, reviewed the various methods of sterilization in women. We are interested primarily in reporting our failures and the reasons for them and not in a discussion of which is the best method.

Pregnancy after tubal ligation is unwelcome in most instances to the patient and her husband and is most disconcerting to the physician. The patient is subjected again to the risks of pregnancy and usually subjected a second time to the risk of a laparotomy.

In this report we are including all the cases in which various methods of sterilization were used, and the number of failures with each. We were impressed by the number of operations designated in various reports as the Madlener method, but which actually bore little resemblance in most instances to the original procedure designed by Madlener. We, too, thought that we had been using the Madlener, but to our surprise found that it was not according to the directions of the author. In the majority of the cases under consideration, the tube was clamped close to the uterus, using until 1944 a heavy Koehrer clamp and then ligating with a silk suture below and above the crushed area of the tube. From 1944 to 1946, we used a Payr clamp, but persisted in crushing and ligating the tube close to the uterus. Since early 1946 we have been following the original Madlener technique as depicted in Fig. 1, crushing the tube in the proximal end of the outer third, and placing one silk or cotton suture in the area of the crush as well as tying through the crushed area. Madlener did not state the length of time he left the angiotribe in place preliminary to ligation, but we have been compressing the tube for one minute. The angiotribe described by Madlener was 7 mm. in width. Our Payr clamp is 8 mm. in width at the base, tapering to 3 mm. We use the widest part. None of the patients ligated since 1946 have to date returned pregnant.

Koller states that in three patients in whom the tubes were ligated near the fimbriated end a hydrosalpinx developed. We have not noted any enlarge-

clinical stage of the lesions in the nineteen cases missed on initial biopsy examination with the seventeen cases missed on the initial vaginal smear.

In this table it is seen that most of the cases missed by the first smear are relatively evenly spread among Stages I, II, and III, and only eight of the seventeen were Stage 0 or I. However, a majority of the cases missed by the first biopsy, fifteen out of nineteen, were early and possibly curable cases. In the preinvasive group alone this comparison is striking. There were a total of sixteen cases of cancer in situ in the 181 cases under study. The first biopsy failed to make a positive diagnosis in eight of these (Table II, Stage 0), but the first smear was positive for cancer in fourteen of the same sixteen cases.

Tables III and IV present details of the cases in which the diagnosis was missed by the first biopsy and first vaginal smear, respectively.

Summary

A comparison of the diagnostic accuracy of the vaginal smear and the standard biopsy technique has been made in 181 cases of epidermoid carcinoma of the cervix. The first biopsy report was correctly positive in 90 per cent of the series. The first vaginal smear report was positive in 91 per cent of the same cases. By a combination of the two methods, the correct diagnosis was initially obtained in 178 cases, or approximately 99 per cent of the group. The vaginal smear was more accurate than the biopsy in diagnosing the early carcinomas of the cervix in this series of cases.

From this study of cervical cancer we conclude: first, that the vaginal smear is diagnostically as reliable as the biopsy taken in a large general hospital; second, that an extremely high percentage of cases can be diagnosed accurately if the two methods are used together; and finally, that the vaginal smear is of especial value in the diagnosis of the very early malignant lesions of the cervix.

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It is not pertinent to our report, but since we have performed a large number of ligations, we are listing our indications for tubal ligation. The following complications or diseases may necessitate the termination of the reproductive career:

Obstetric: (1) Vascular-renal disease, (2) repeat cesarean section, and (3) repetition of major fetal abnormalities such as erythroblastosis.

Medical: (1) Heart disease, (2) diabetes mellitus or insipidus, (3) pulmonary tuberculosis, active or healed, but with extensive pathology, (4) neurologic and psychiatric disease, and (5) certain blood dyscrasias. Multiparity in association with minor medical or obstetric complications may justify tubal ligation. (The couple should have at least three healthy children.) (1) Epilepsy, particularly if there is a history of epilepsy in the family, (2) incapacitating varicosities of the vulva or lower extremities. (3) otosclerosis, (4) mental deficiency in either partner, (5) anxiety states resulting from the fear of future pregnancies, and (6) failure or the inability to use the usual methods of birth control.

We recognize the hazards of entering into the sociologic aspects of the problem of sterilization, particularly in regard to the justification of the procedure used with multiparity as the sole indication. However emphatically we may believe in the limitation of the family to that number of children which can be adequately cared for in that particular income level, *we have always insisted that there be some medical or obstetric indication for the interruption of future childbearing.*

TABLE I

	TOTAL NUMBER OBSTETRIC PATIENTS	PATIENTS STERILIZED (PER CENT)	STERILIZED AT CESAREAN SECTION (PER CENT)
C. Lull—Philadelphia Lying-In, 1924-1933	14,039	1.3	49
R. Knight—Sloane Hospital, 1934-1944	16,266	1.4	43
F. Irving—Boston Lying-in, 1934-1944	45,216		24
Chicago Lying-in, Jan. 1935-July 1945	31,930*	3.6†	48

*Including: vaginal deliveries, cesarean sections, patients with hysterectomy for purpose of therapeutic abortions, Porros.

†Including hysterectomies for purpose of therapeutic abortion and sterilization, and Porro or cesarean hysterectomies.

The data in Table I illustrate the incidence of tubal ligation on our service in the period under consideration. The explanation for the variance in our statistics from those of other services is undoubtedly to be found in the large group of multiparas, women with four or more children who present concomitantly a justifiable medical or obstetric indication for interruption of future childbearing. We suggest tubal ligation at the time of the second cesarean section and become insistent at the third cesarean section; however, *our policy now does not include the performance of cesarean section for the primary purpose of sterilization.*

Our statistics as presented in Table II are unfavorable. However, it must be remembered that our service is primarily a teaching one, and that though our staff patients are directly supervised by the senior staff departmental member,

ment of either tube in those patients who became pregnant after ligation and were again subjected to operation. Perhaps there are some changes in the tube adjacent to the uterus if the ligation is in the outer third, but, if so, these changes should increase the safety of the tubal ligation. The senior author has, in a number of cases, crushed and ligated the tube near the fimbriated end and then injected either 95 per cent alcohol or sodium morrhuate into the wall of the tube adjacent to the uterus. He has not used this routinely, but it certainly increases the safety of the operation.

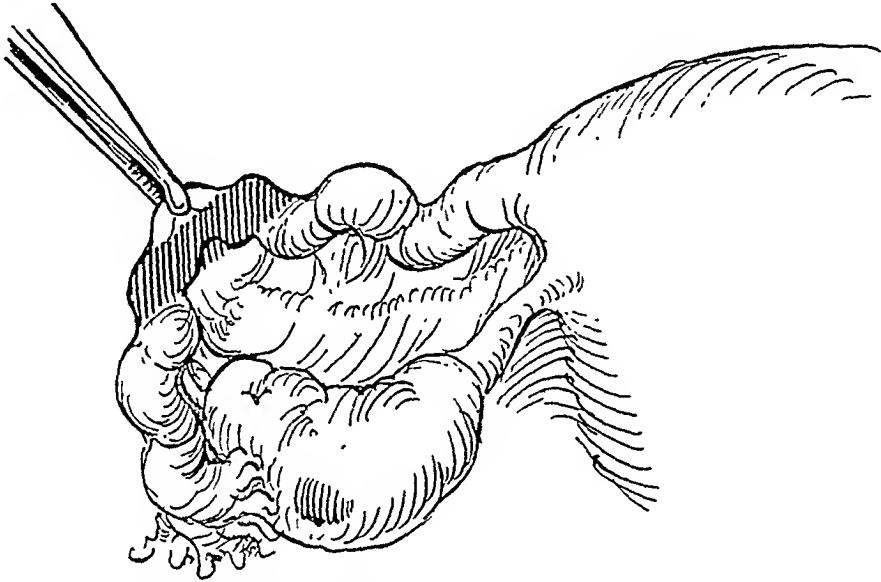


Fig. 1.—Loop in outer one-third of tube is crushed with Payr clamp for one minute and then ligated with silk or cotton suture. Care must be taken not to tie too tightly.

We have maintained that the simplest and most nontraumatic attack on the Fallopian tube is the procedure of choice; particularly is it justified if the results of this procedure are comparable to those of more extensive operative procedures. We are presenting cases of failed tubal ligations, performed either as a twenty-four-hour postpartum procedure or in conjunction with other operative obstetric or gynecologic procedures. We have made no attempt to follow every patient who submitted herself for a tubal ligation, but have collected our data from the records of patients who have returned to us with a pregnancy following a ligation. We believe that we have, in this way, overlooked few failures for the well-recognized experience that these patients in whom ligations have failed are analogous to the vindictive customer who "wants her money back," and returns to demand it or to be reassured that she can't possibly be pregnant.

Unfortunately, we were unable to examine the site of ligation directly to ascertain the cause of failure in all of our cases, but in those who returned for a subsequent laparotomy the failures could be ascribed to either mistaken identity (one case) where the round ligament was ligated or to cases where the tubes were ligated but the lumen re-established, presumably as a result of an excessive constriction of the ligature which had either sheared or completely severed the tube.

Of less pertinence, but of some interest, are other minor data recovered in an analysis of our series. The minimum period between tubal ligation and subsequent pregnancy has been two months, the maximum thirty-nine months, and the average fourteen months. The fertility of this group of patients ranged from a minimum of two pregnancies to a maximum of nine, the average 4.1. Lactation did not appear to be of significance: sixteen patients did not nurse, six did, and on eight patients no relevant information was obtainable. The youngest patient at the time of the tubal ligation in whom a failure occurred was 20 years, the oldest 43 years, and the average age was 28.3 years.

If the operative technique of tubal ligation has been carefully explained to the patient and her husband, there will be no psychic changes and no loss of libido. The menopause will not develop at an earlier age if the venous return from the ovary and tube is not obstructed.

Summary

We believe that the Madlener method of tubal crushing and ligation will prevent future pregnancies if it is properly carried out. It is the simplest and safest surgical procedure and can be performed at the time of a gynecologic operation, at the time of cesarean section, at the time of interruption of pregnancy by the abdominal route or as the twenty-four-hour procedure as advocated by our clinic.

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TABLE II. MADLENER STERILIZATIONS

	NUMBER	FAILURES CASES	PER CENT
Von Graff (Collective review to 1938)	4,279	19	0.44
Adair and Brown	50	0	0
Dippel	101	5	4.9
Hewitt and Whitley	100	0	0
Pfeutze	165	3	1.9
Dieckmann-Hauser	912*	33†	3.6

*Majority were Madlener.

†All Madlener; one tubal resect.

TABLE III

FROM JANUARY 1, 1935 TO JULY 1, 1935	NUMBER OF CASES	NUMBER OF FAILURES	PERCENTAGE OF FAILURES
Cesarean section and tubal ligation	418	14	3.3
Twenty-four-hour tubal ligation	286	16	5.6
Abdominal tubal ligation (Gynecologic)	93	0	0
Hysterotomy and tubal ligation	77	1	1.3
Vaginal tubal ligation	38	2	5.2
Total	912	33	3.6%

the tubal ligations are usually done by the senior obstetric resident. The higher incidence of failures in the staff as compared to the private patients supports our belief that the competent surgeon need have a negligible incidence of failures. One of our senior staff members over a period of two odd decades has had no known failures in a sizeable series of his private patients.

When we analyze the failures of sterilization combined with another operative procedure or as a twenty-four-hour postpartum procedure we find as in Table III that one of our highest numbers of failures is found in the group of vaginal surgery, usually a vaginal plastic in combination with a tubal ligation from below. This is not surprising, as the difficulties encountered in adequate exposure are obvious in this manner of approach to the Fallopian tubes. Nor were we particularly surprised by the rather high incidence of failures in the twenty-four-hour postpartum group, for this is the group which is handled primarily by the senior resident, as are the ligations incident to the cesarean section group, where the senior staff member usually drops out, permitting the resident to perform the ligation and closure. It is of interest to note the lack of failures of ligations in combination with a laparotomy for gynecologic indications. One wonders whether the tube, altered by the normal pregnancy tissue changes, is less amenable to permanent closure or is so edematous and friable that the utmost of delicacy in the manipulation and ligating is necessary to prevent a cutting or shearing of the ligature and subsequent fistula formation.

We doubt that morbidity plays a significant role as a cause of failure inasmuch as the morbidity in the series of failed ligation incident to cesarean section or as a postpartum procedure did not differ appreciably from our overall morbidity for cesarean sections and vaginal deliveries.

TABLE II. MORBIDITY DUE TO GENITAL TRACT INFECTION

YEAR	TOTAL DELIVERIES	NUMBER OF CASES OF GENITAL TRACT INFECTION	PER CENT
1946-1947			
July to Mar., 1947	1,573	60	3.8
Penicillin	778	18	2.3
No penicillin	795	42	5.3

There were 1,573 cases in the series (Table II); 778 received 200,000 units of penicillin in the form of cocoa butter suppositories inserted into the posterior fornix of the vagina with a sponge forceps immediately following delivery. There were 795 cases used as controls who received no penicillin. From January to June, inclusive, 1946, there were 1,434 deliveries. There were 80 cases of genital tract infection, or a morbidity rate of 6.7 per cent. The series of 1,573 was begun in July, 1946, and continued through the middle of March, 1947. There were 60 cases of genital tract infection, or 3.8 per cent morbidity for this group. Of the 778 patients receiving penicillin vaginal suppositories, 18, or 2.3 per cent, developed genital tract infection. Forty-two of the 60 patients developing morbidity were in the untreated group of 795 cases. Thus the morbidity rate for this latter group was 5.3 per cent.

Of the 18 patients developing genital tract infection who received penicillin, 14, or 77.7 per cent, had either episiotomy or lacerations repaired. Of the 42 patients who developed infection who did not receive penicillin, 20 cases, or 47.8 per cent, had either laceration or episiotomy. In the entire group 428 cases, or 55 per cent, of those patients receiving penicillin post partum had either episiotomy or lacerations. In the control groups, 357 patients or 44.9 per cent, had either episiotomy or laceration. Thirty-four, or 56.6 per cent, of the patients developing morbidity had either episiotomy or laceration.

Statistical study of the effect of these complications is not warranted when the control or alternate case method is considered. The difference between the treated (2.3 per cent) and the untreated (5.3 per cent) is statistically significant.

Penicillin blood levels were tested on 49 patients. The Randall, Welch, and Price method was used with *B. subtilis*, the test organism. Eleven cases failed to develop blood levels. Thirty-eight cases had blood levels averaging 0.06 units per c.c. of serum in one-half hour, 0.06 to 0.25 units at one hour, and 0.06 to 1.00 at two hours. All but five cases who had levels, maintained them for at least two hours. The two-hour levels on these five showed no penicillin. The absorption seemed to depend somewhat on the amount of bleeding post partum plus the vigorous massage of the fundus which some patients inevitably receive.

It is regrettable that funds were not available for adequate blood levels to learn if local or general effects were obtained and to establish the dosage.

Summary

1. Seven hundred and seventy-eight of 1,573 cases in the group received 200,000 units of penicillin per vaginam immediately after delivery with a morbidity rate due to genital tract infection of only 2.3 per cent.

2. In the control group of 795 cases, the morbidity rate corrected was 5.3 per cent.

3. The morbidity rate of 3.8 per cent for the entire group of 1,573 cases was considerably less than the 6.7 per cent rate encountered in the first half of 1946, and the average of 7.84 per cent for the past ten years.

4. Blood levels were obtained with intravaginal penicillin in 77.5 per cent of cases on which levels were tested.

PENICILLIN VAGINAL SUPPOSITORIES AND THE PREVENTION OF POSTPARTUM MORBIDITY

ROBERT R. PIERCE, M.D., CINCINNATI, OHIO

(*From the Department of Obstetrics, Cincinnati General Hospital*)

PUERPERAL infection has been one of the leading causes of maternal death for many years. In recent years, death from infection has been greatly reduced since the introduction of the sulfonamides and antibiotic drugs. However, morbidity during delivery and the puerperium has not decreased in a like manner.

In a teaching institution such as the Cincinnati General Hospital, there are many individuals involved in the preparation, delivery, and aftercare of women entering the hospital for obstetric care. Contamination before, during, and after delivery undoubtedly accounts for a large proportion of morbidity in obstetric cases. Morbidity reports from various centers throughout the country range from approximately 3.3 per cent corrected to as high as 10.5 per cent corrected. Our own morbidity figures (Table I) range from a low of 5.7 per cent in 1941 to a high of 10.3 per cent in 1944. The average morbidity due to genital tract infection was 7.84 per cent from 1936 to 1945, inclusive.

TABLE I. MORBIDITY DUE TO GENITAL TRACT INFECTION

YEAR	TOTAL DELIVERIES	NUMBER OF CASES OF GENITAL TRACT INFECTION	PER CENT
1936	2,114	123	5.8
1937	2,252	183	8.1
1938	2,497	201	8.1
1939	2,484	171	6.9
1940	2,542	181	7.1
1941	2,630	151	5.7
1942	2,604	218	8.3
1943	2,282	206	9.0
1944	1,835	188	10.3
1945	1,885	171	9.1
1946			
1947, Jan. to June	1,434	80	6.7

Since infected cases require isolation, increased nursing care and increased time in the hospital and, believing that most of the infection was exogenous and occurred during labor and delivery, it was decided to use penicillin locally in the form of vaginal suppositories* containing 100,000 units of penicillin each. The alternate case method was chosen, and only cesarean section cases were excluded. The standard method for determining morbidity was used. The figures have been corrected, and include only cases of genital tract infection associated with episiotomy or laceration, endometritis, parametritis, and pelvic thrombophlebitis. There were no cases of thrombophlebitis of the lower extremities. Infinite care is taken by the staff of this service in making the diagnosis. Morbidity is based on a temperature elevation to 100.4° F. any two days following the first day of the puerperium.

*Penicillin Vaginal Suppositories furnished by Schenley Laboratories, Inc.

MALIGNANT GRANULOSA-CELL TUMOR IN AN INTRASPLENIC OVARIAN GRAFT IN A CASTRATED MALE MOUSE*

MIN HSIN LI,† PH.D., NEW HAVEN, CONN.

(From the Department of Anatomy, Yale University School of Medicine)

GRANULOSA-CELL tumors and luteomas have developed in intrasplenic ovarian grafts in castrated male and female mice.^{1,2} More recent experiments showed that ovarian tumors have also formed in intrapancreatic ovarian grafts in castrated mice.³ It is assumed that the prolonged stimulation by augmented amounts of gonadotrophic hormones of the hypophysis, to which the ovaries are subjected in this site, is responsible for the development of the neoplastic growths. In our previous studies, mitotic activity of the granulosa tumor cells and indications of invasion into the splenic tissues were observed in the tumors, although metastases were not noted and the tumors were not transplanted to determine the capacity for progressive growth in a new host. This paper is a report of metastasis and successful transplantation of a granulosa cell tumor.

Male and female mice of the A, C₃H, and C₅₇ strains, and several groups of hybrid mice (A X C₃H and CBA X C₅₇) were used. They were castrated, and received, at the same time, an autoplasmic or homoplasmic ovarian graft in the spleen. Some of them were given subcutaneously weekly injections of 16 micrograms alpha-estradiol benzoate, 1.25 mg. testosterone propionate, or 1 mg. progesterone. Unilaterally gonadectomized mice with intrasplenic grafts served as controls. The experiments extended for a period of ten months.

Observations

Ovarian tumors appeared in intrasplenic ovarian grafts in mice of the A, C₃H, and C₅₇ strains, and in hybrid mice. There is apparently no strain limitation in the development of tumors in autotransplants or homotransplants of ovaries in castrated mice. Ovarian tumors have not been observed in intrasplenic ovarian grafts in unilaterally gonadectomized male and female mice. The formation of tumors in intrasplenic ovarian grafts did not occur in mice receiving weekly administration of estradiol benzoate or testosterone propionate beginning fourteen to nineteen weeks after the ovaries were transplanted. Treatment with progesterone, however, was not effective under similar conditions.

Among 17 castrated male and female mice treated with progesterone, eight granulosa cell tumors, one luteoma, and three mixed cell tumors (granulosa and luteoma cells) were found in intrasplenic ovarian grafts from 213 to 284 days old. One nontumorous graft was one hundred and ninety-three days old. No tumor was noted in four grafts with vascularized adhesions that permitted drainage through other than the hepatic portal system. Metastasis of one granulosa-cell tumor into the liver was observed in a castrated male mouse of

*Presented at the Annual Meeting of the American Association for Cancer Research, May 16, 1947, at Chicago, and the New England Cancer Society, May 23, 1947, at New Haven, Conn. This research has been aided by grants from The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

†The Anna Fuller Fund Fellow in Anatomy.

5. No local or systemic reactions were noted.

6. There was no definite relationship between development of morbidity and perineal wounds.

Conclusions

1. The use of penicillin in the form of vaginal suppositories at the time of delivery definitely reduced the puerperal morbidity rate on our service.

2. This preparation should be of particular value in cases which become morbid after early rupture of membranes, long labor, and where genital tract infection is suspected.

3. The use routinely of penicillin vaginal suppositories after delivery is justified because of the reduction of the nursing care required, in infected cases, reduction in number of extra hospital days required per patient, and particularly a reduction in genital tract infection following delivery.

I wish to express my appreciation for the valuable suggestions given to me by Dr. Marion A. Blankenhorn, Professor of Medicine, and Dr. Morton F. Hamburger in the preparation of this publication, and to Dr. Ralph Heery for his aid in the laboratory work.

small metastatic foci were observed. Abdominal ascites and pleural effusion were present. The small urinary bladder was distended with urine, and the seminal vesicles and prostates were atrophic. Other visceral organs and pituitary gland appeared normal.

Microscopic examination revealed that the tumor was incompletely encapsulated and composed of compact masses of granulosa tumor cells showing numerous mitotic figures (Fig. 1). Some masses of tumor cells, however, were arranged in a folliculoid pattern. The germinal epithelium of the tumorous graft showed no extensive ingrowth. Luteinized cells and small necrotic areas were observed at the periphery. A spicule of bone was found at the junction between tumor and splenic tissue (Fig. 2), but in an area showing no necrosis. The metastatic granulosa tumor cells in the liver were aggregated in nodular masses situated adjacent to hepatic sinusoids or veins (Fig. 3). Each large, solitary granulosa-cell mass exhibited histologically a miniature of the primary tumor in the spleen (Fig. 4). The nuclei of tumor cells were hyperchromatic, and mitoses were common.

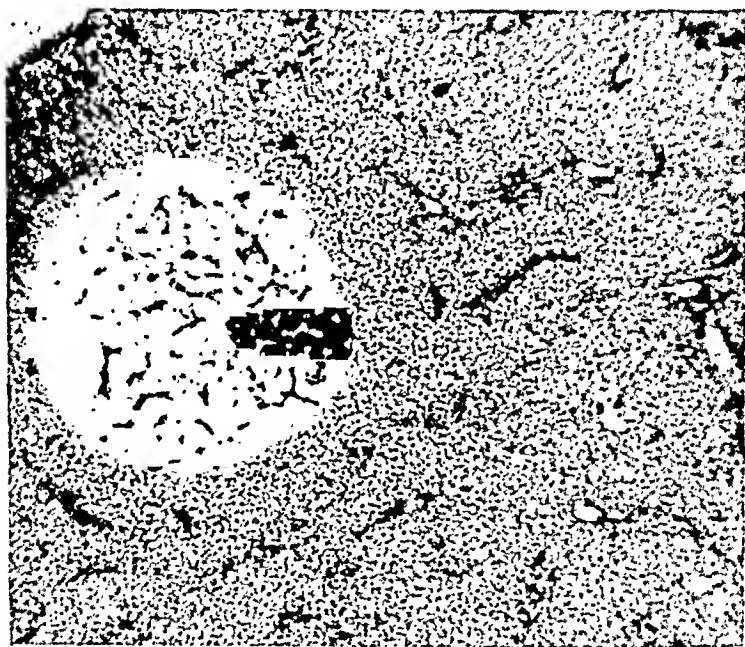


Fig. 3.—A metastatic nodule of the granulosa cell tumor in the liver. ($\times 30$, approx.)

The granulosa cell tumor was transplanted by inserting small fragments subcutaneously along the right lateral body wall through a thirteen-gauge hypodermic needle fitted with a plunger. Ten mice (six castrated males, two castrated females, and two intact males) of the A strain, one castrated female mouse of the C_3H strain, and two castrated female mice of the CBA strain were used as hosts. All of them received four weekly injections of 1 mg. progesterone subsequent to the transplantation. Progressive growth of transplanted tumors was noted in one castrated female mouse of the A strain, and in two castrated male mice of the same strain.

The castrated female host was killed seventy-three days after the transplantation. Constant estrous vaginal smears were noted during the last thirty days; and the uterus weighed 120 mg. at autopsy. The transplanted tumor was very well vascularized, and measured 12 by 20 by 22 mm. in diameter. Histologically, the transplanted tumor resembled the original tumor (Fig. 5), except that some of the folliculoid masses contained hemorrhagic cavities.

the A strain bearing an intrasplenic graft for two hundred and thirteen days. This animal had received nine weekly subcutaneous injections of 1 mg. progesterone dissolved in sesame oil starting one hundred and thirty-eight days after the grafting. The tumorous graft was reddish yellow, solid and measured 14.5 by 15 by 21 mm. in diameter. The tumor received a collateral vascular supply from the pancreas. The spleen was normal in size, but most of the distal portion merged into the tumor. The liver was brownish red in color, and several



Fig. 1.—Section of a granulosa cell tumor in an intrasplenic ovarian graft (213 days) in a castrated male mouse. ($\times 85$.)

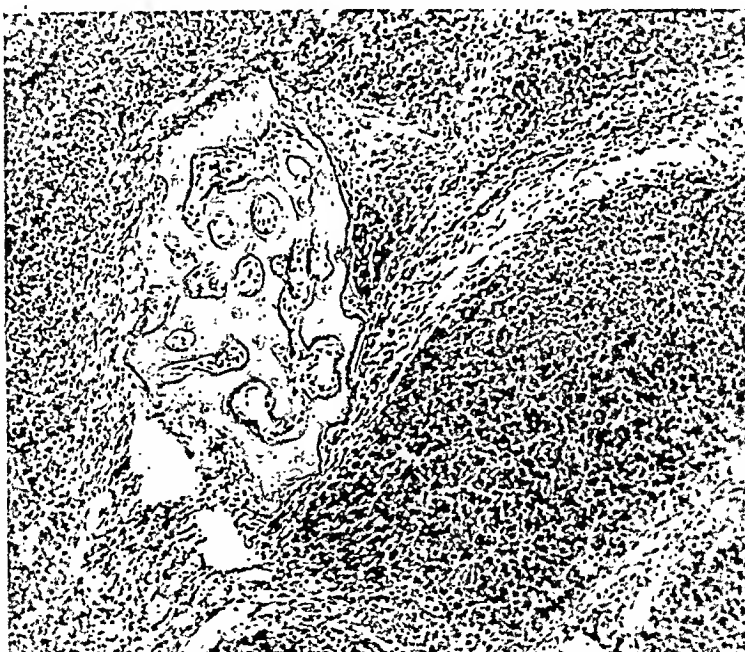


Fig. 2.—Section showing a spicule of bone at the junction between the tumor and splenic tissue (left side). ($\times 85$.)

Discussion

The administration of progesterone in weekly doses of 1 mg. did not inhibit tumor formation in intrasplenic ovarian grafts in castrated mice. On the other hand, the doses of estradiol benzoate and testosterone propionate, and endogenous hormones from one intact gonad exerted an inhibitory influence.

The first granulosa-cell tumor successfully transplanted in a mouse arose spontaneously in an untreated animal, and the transplanted tumors secreted estrogen.⁴ The ability of metastasis and transplantability in new hosts indicated the malignancy of granulosa-cell tumors developed in intrasplenic ovarian grafts. In this respect the tumors resembled ovarian tumors developed in the ovaries of x-rayed mice.⁵

Summary

A transplantable granulosa cell tumor with metastasis in the liver developed in an intrasplenic ovarian graft in a castrated male mouse. The present experimental result indicated that granulosa cell tumors induced in intrasplenic ovarian grafts may become malignant growths.

Grateful acknowledgment is made to Dr. E. Schwenk of the Schering Corporation for the alpha-estradiol benzoate (Progynon-B), testosterone propionate (Oreton), and progesterone (Proluton); and to Dr. E. Oppenheimer of the Ciba Pharmaceutical Products, Inc., for the progesterone. .

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The transplanted granulosa cell tumor from the castrated female host was further inoculated subcutaneously into ten castrated male and female mice of the A strain, but progesterone was not injected. The transplants in the second passage are growing rapidly in all of the hosts.

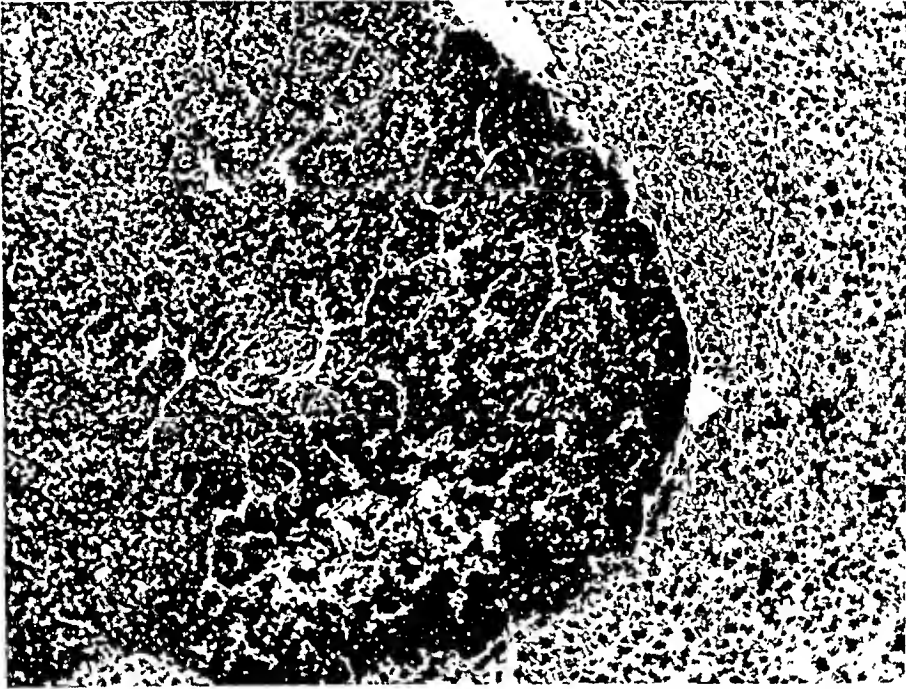


Fig. 4.—Higher magnification of metastatic granulosa tumor cells in the liver. ($\times 180$.)

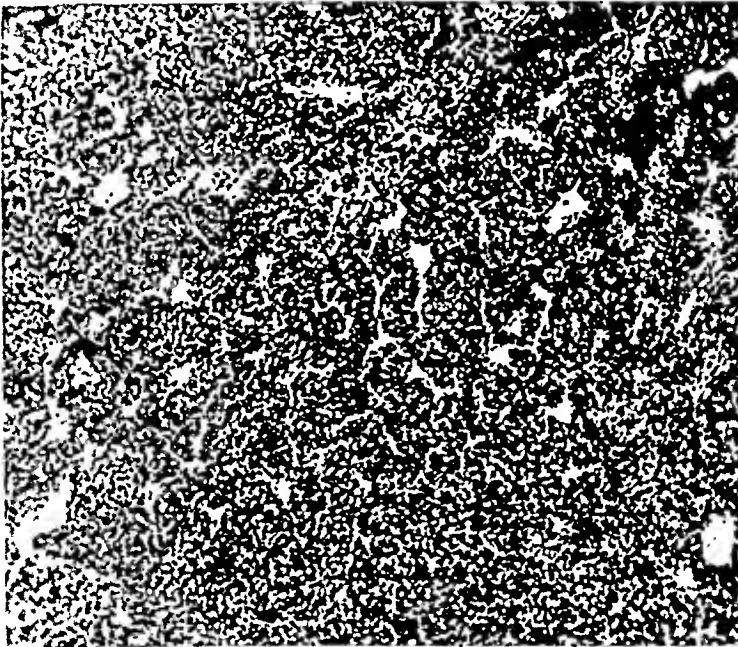


Fig. 5.—Section of a subcutaneously transplanted granulosa cell tumor (73 days) in a castrated female mouse. ($\times 90$.)

Pre-eclampsia

Three hundred seventy-eight patients had pre-eclampsia in at least one pregnancy. Sixty of these women had pre-eclampsia with more than one pregnancy. The pre-eclamptic toxemias were listed as mild or severe according to the criteria advanced by the American Committee on Maternal Health. Of the 275 cases classified in the mild group, seventy (25.4 per cent) had hypertension subsequent to the toxemia. Among the 103 severe cases, residual damage occurred in forty-four (42.7 per cent). When these two groups are combined, making a total of 378 patients with pre-eclampsia, the incidence of residual damage is found to be 30.1 per cent (114 cases).

The time that elapses from the onset of the first signs and symptoms of a toxemia to termination of the pregnancy, in other words duration of toxemia, has been emphasized repeatedly as a dominant factor in the incidence of residual damage.¹⁻⁷ The statement has been made that toxemia should not be allowed to persist for more than three weeks because of the increased danger of late damage.⁸⁻¹⁰

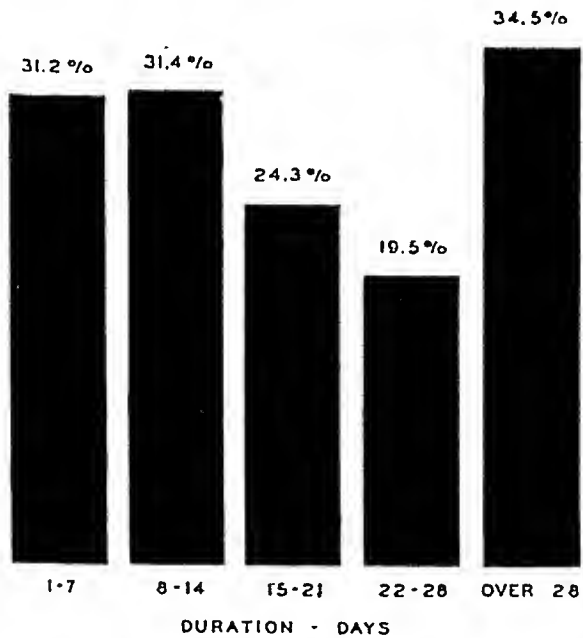


Fig. 1.

Hence we have grouped all of our patients with pre-eclampsia according to duration of the toxemias as follows: one to seven, eight to fourteen, fifteen to twenty-one, twenty-two to twenty-eight, and over twenty-eight days. The result of this grouping is shown clearly in Fig. 1. It is seen that *residual damage does not increase progressively with increased duration of the toxemia*. When the toxemia was allowed to run for one to seven days, late damage occurred in 31.2 per cent of 128 cases; eight to fourteen days in 31.4 per cent of 54 cases; fifteen to twenty-one days in 24.3 per cent of 37 cases; twenty-two to twenty-eight days in 19.5 per cent of 46 cases, and over twenty-eight days in 34.5 per cent of 113 cases. The incidence of late damage is highest in that group in which the toxemia persisted for longer than four weeks. Yet it is only slightly higher than it is in the one-week or the two-week groups, whereas it is considerably higher than it is in the three- and four-week groups.

The cases were also grouped according to age at the time of the pre-eclamptic pregnancy. If a patient had toxemia with more than one pregnancy,

A NINE-YEAR FOLLOW-UP IN CASES OF TOXEMIA OF PREGNANCY*

FRANK P. LIGHT, M.D., BROOKLYN, N. Y.

*(From the Department of Obstetrics & Gynecology of the Long Island College of Medicine,
Long Island College Hospital Division)*

THE toxemia clinic was established at the Long Island College Hospital in September, 1937. To this clinic are referred all prenatal patients showing evidence of a developing toxemia of pregnancy. Also referred to this clinic are all patients with a history of a toxemia in a previous pregnancy whether it occurred in our institution or elsewhere, as well as those patients who have a history or evidence of vascular-renal disease. All patients are encouraged to return to this clinic at periodic intervals after delivery in the hope that we may be able to evaluate the effects of the toxemias upon these patients in later life as well as in subsequent pregnancies.

This study is based on a review of the records of 391 women of a total of 530 toxemia clinic patients who were carried through 968 pregnancies. Six hundred eighty-five of these pregnancies were associated with toxemia or vascular-renal disease. The remaining 283 pregnancies were normal following a previous toxemia.

Of the 391 patients who exhibited true toxemia of pregnancy, thirteen had eclampsia, 275 were classified as pre-eclampsia mild, and 103 as pre-eclampsia severe. This report is limited to an analysis of the late results in this particular group of patients, and is concerned chiefly with the incidence of residual damage. The most common evidence of residual damage is an elevated blood pressure. In only a few cases, with the tests at present available, has there been shown to be any definite renal impairment. Three hundred three patients in this group were seen on one or more occasions after discharge from the hospital, the period after delivery varying from a few weeks to a number of years, the longest follow-up period being nineteen years in one patient. In the remaining cases, the diagnosis of residual damage or its absence is of necessity based upon the blood pressure course and blood and urine studies made in the hospital in the immediate puerperium.

Eclampsia

The records of only thirteen cases of eclampsia have been encountered in this study, too small a group to warrant the drawing of any conclusions. However, it is of interest that four of these (30.7 per cent) showed evidence of residual damage. All but one of them occurred in the first pregnancy. All were under 25 years of age. The presence of residual damage was based on follow-up study of three months in two, three years in one, and five years in the fourth. The shortest follow-up period in those without residual damage was three years, the longest seventeen years, and all were followed through subsequent pregnancies.

Two other patients gave a history of having had eclampsia previously, were followed through another pregnancy in our clinic, and showed no evidence of residual damage at four and seven years, respectively.

*Read, by invitation, before the New York Obstetrical Society, March 11, 1947.

tensive pregnancy, four of these patients were between 20 and 25 years of age, five between 26 and 30 years, ten between 31 and 35 years, and thirteen over 35 years. In one, the age was not stated.

There was another group of patients, eleven in number, whose records showed pre-eclampsia followed by one or more perfectly normal pregnancies,

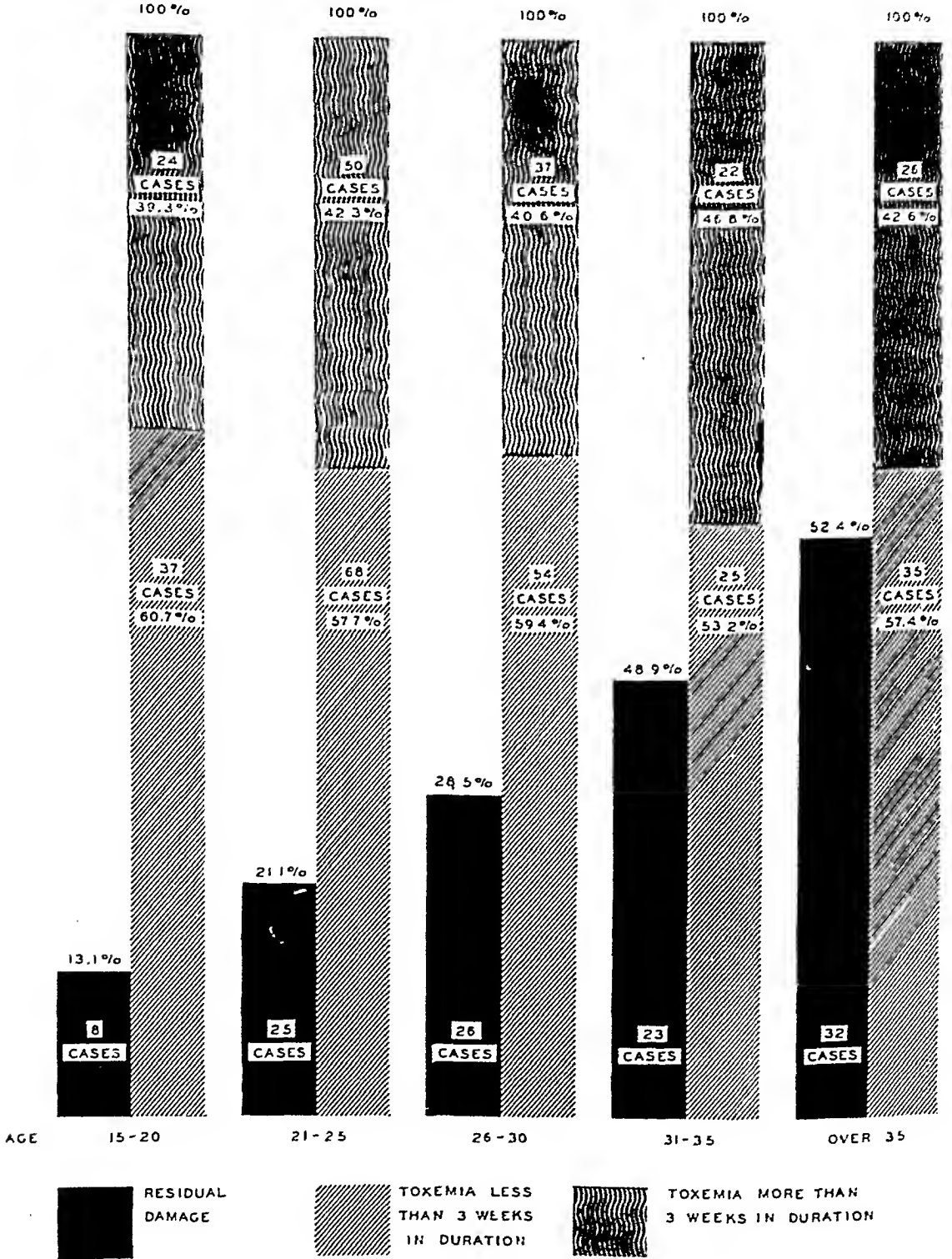


Fig. 3.

as sixty did, she was listed according to her age with her first toxemia. Fig. 2 shows the results of this grouping. There is seen to be a *definite relationship between age at the time of the toxemia and the incidence of residual damage. Late damage increases progressively with age.* At the age of fifteen to twenty years 13.1 per cent of 61 cases showed late damage; at twenty-one to twenty-five years, 21.1 per cent of 118 cases showed such damage; at 26 to 30 years, damage occurred in 28.5 per cent of 91 cases; at 31 to 35 years, in 48.9 per cent of 47 cases and over the age of 35 years, 52.4 per cent of 61 patients showed evidence of residual damage. Table I gives the number of patients in each age and in each duration group.

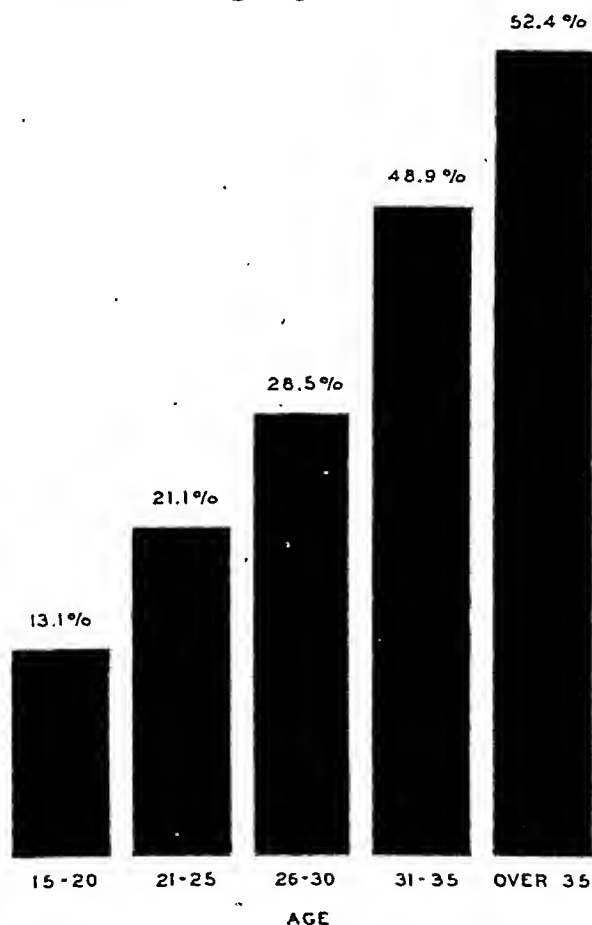


Fig. 2.

Fig. 3 shows again the incidence of residual damage in each age group. It also shows the percentage of patients in each group in which duration of the toxemia was less than three weeks and over three weeks. As may be observed, the percentage of patients in whom the toxemia lasted three weeks or longer is almost the same for each age group. It would seem, therefore, that *age, rather than the duration of the toxemia, is the determining factor.*

The finding of hypertension in a patient who has had pre-eclampsia several months or years before often leads to the conclusion that this is evidence of residual damage. How many of these women would have had hypertension at a given time in life, even though they had never been pregnant? The importance of this question was emphasized by a group of thirty-three patients with hypertension complicating pregnancy. All of these thirty-three women had been pregnant before, and all of their previous pregnancies were known to have been normal. At the time of the hyper-

HEPARIN IN THE TREATMENT OF TOXEMIA OF PREGNANCY

A Preliminary Report

J. VAN S. MAECK, M.D., AND H. ZULLACHTS, M.D., NEW YORK, N. Y.

(From the Obstetrical Clinic, Woman's Hospital)

THE pathologic changes which are found in women who die from toxemia of pregnancy are frequently neither consistent nor pathognomonic. However, numerous writers have observed certain changes which occur with quite some regularity. These, in general, consist of diffuse scattered capillary or arteriolar lesions in different organs.¹ The presence of thrombi in these vessels, and the frequency of isoagglutination reactions in pregnant patients, not infrequently observed, has impressed the authors of their probable importance in the pathogenesis of toxemia of pregnancy.

In 1902, Flexner² demonstrated the presence of agglutinated erythrocytes associated with thromboses in the smaller vessels of the liver, and observed that these were in the neighborhood of the areas of necrosis and hemorrhage. Dienst, in 1905,³ suggested that fetal erythrocytes reached the maternal circulation, and there gave rise to agglutination. Boyd⁴ states that symmetrical cortical necrosis, as seen occasionally in eclamptics, is caused by thrombosis of the interlobular arteries and afferent arterioles. Yamada⁵ has suggested or hinted that toxemia of pregnancy is due to allergy and some special sensitization related to a toxin. That isoagglutination is much more common in pregnant women, and especially so in those with eclampsia, has been stated by Dexter and Weiss,⁶ and noted by others.

The probability that the peripheral necrotic lesions at times observed in eclamptic patients are due to vascular thrombi is suggested by Dexter and Weiss.⁷ They have considered the explanation to lie in the character of the hepatic circulation: The liver cells receive nourishment from the hepatic sinusoids whose blood is obtained from branches of both portal vein and hepatic artery. However, some of the interlobular branches of the hepatic artery supply directly the peripheral zone of the lobule with capillaries, and since the liver cells depend on their oxygen supply from the capillaries of the hepatic artery, thrombosis of these individual vessels lead to infarction.

M. Knisely⁸ first observed agglutination of red blood cells in the conjunctival vessels of an eclamptic patient. Working along this same line of investigation, Odell, Aragon and Pottinger observed this phenomenon in several patients with eclampsia and have described this condition of intravascular clotting as "sludged" blood. They consider these findings of particular importance.⁹

Dieckmann¹⁰ states in his monograph on the *Toxemias of Pregnancy* that the fibrinogen concentration in the blood averages 0.26 in nonpregnant individuals, whereas in pregnancy it is definitely increased to an average of 0.48 at term, with a range of 0.3 to 0.7 Gm. per cent. In eclampsia he has stated that the fibrinogen content of the blood occasionally exceeds 1 per cent in concentration. He and Schwarz have postulated that the lesion of eclampsia could be produced by substances entering the portal circulation from the intestine. They

TABLE I

AGE (DAYS)	NO RESIDUAL DAMAGE					WITH RESIDUAL DAMAGE				
	1-7	8-14	15-21	22-28	OVER 28	1-7	8-14	15-21	22-28	OVER 28
15-20	16	9	5	5	18	4	1	2	0	1
21-25	36	8	12	11	26	8	4	0	1	12
26-30	20	6	9	15	15	12	6	1	3	4
31-35	6	5	2	4	7	7	3	2	0	11
Over 35	10	9	0	2	8	9	3	4	5	11

which were in turn followed by a pregnancy associated with hypertension. These eleven patients may be listed, as they were in this study, as showing residual damage, latent perhaps, due to the previous pre-eclampsia. On the other hand, it might well be that these eleven patients would have had hypertension at this particular time in life had all of their previous pregnancies been normal, or even had they never been pregnant.

Summary

A study has been made of the records of 530 patients seen in the toxemia clinic of the Long Island College Hospital. These 530 patients had 968 pregnancies, of which 685 were associated with toxemia or vascular-renal disease, and 283 were normal.

Three hundred ninety-one patients showed evidence of true toxemia of pregnancy. These form the basis of this report.

This study indicates that duration of the toxemia has little bearing upon the incidence of residual damage.

It shows however, that age is a more important factor, the incidence of residual damage progressively increasing with the age of the patient.

The validity of the assumption that hypertension occurring after a toxemia is due to residual damage is questioned.

Evidence is given in support of the conclusion that such hypertension in some cases would have occurred had the patient never become pregnant.

I wish to thank Doctor Alfred C. Beck for the privilege of conducting the Toxemia Clinic and to acknowledge my gratitude to Doctor Mervyn V. Armstrong and the other members of the obstetrical and gynecological staff for their cooperation in the study and management of these toxemia patients.

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mg. per cent, the uric acid 2.8 mg. per cent, and the carbon dioxide combining power 55.7 volumes per cent. The blood type was B, Rh positive, and the prothrombin time normal.

The patient was treated with 20.0 c.c. of 10 per cent magnesium sulfate, and 50.0 c.c. of 50 per cent dextrose intravenously repeated for two days, and, in addition, was given phenobarbital, morphia, colonic irrigations, high protein diet, etc. The response to this treatment was gradual improvement, manifested by progressive lowering of the blood pressure, which finally reached less than 140/80 on the sixth day (Fig. 1). During this time, the urinary albumin varied from day to day (0.2 to 0.8 Gm. per liter) and persisted until her discharge (Fig. 2). The subjective symptoms paralleled the laboratory findings; headache and edema continued until the seventh day. On the eighth day a sudden episode of vaginal bleeding was noted, though this subsided rapidly and she was discharged improved on March 7, 1947.

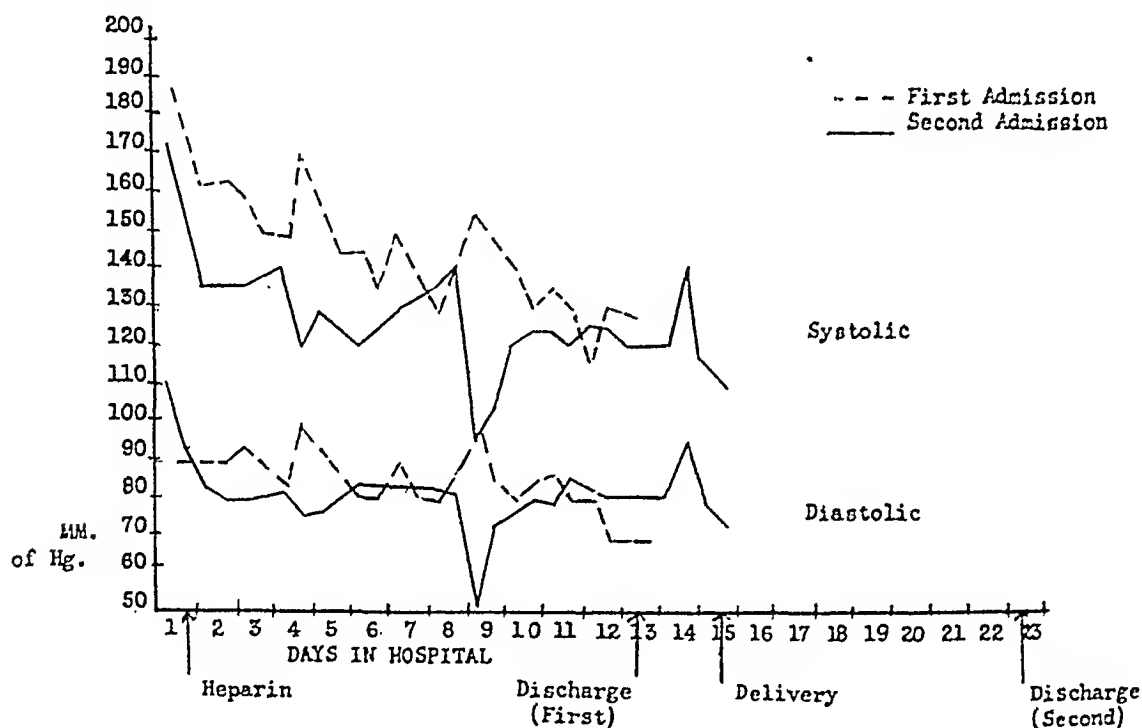


Fig. 1.

The patient was examined every two days in the outpatient clinic thereafter until March 31, during which time she developed progressive hypertension and an increased amount of urinary albumin. On this latter date, she was readmitted because of blurred vision, headache, some edema, and blood pressure of 170/110.

After six hours of bed rest, the blood pressure was 156/94. Physical examination showed slight edema of the feet, ankles, and upper extremities. The ocular fundi were unchanged, as was the remainder of the physical examination, except for the growth of the pregnancy. The catheterized urine at this time showed 1.6 Gm. per liter of albumin, and in addition masses of red blood cells and a few hyalin and granular casts which had not been present on the original admission. The urea nitrogen was 11.8 mg. per cent, and uric acid, 4.1 mg. per cent.

Since it had not been decided to use heparin in the treatment of toxemia when this patient was admitted, she again received intravenous glucose at 3, 6, and 9 P.M. on the day of admission, and again at 4:45 A.M. the following morning. In addition, magnesium sulfate was given at 6 P.M. and 4:45 A.M. the

suggest that these substances (including tissue fibrinogen or the like) could cause a decrease in the coagulation time of the blood in the portal system because the factors normally present to neutralize these substances are relatively decreased in the process of neutralizing chorionic tissue fibrinogen. Such decreased coagulation time would predispose to thrombosis in the portal vein or liver sinusoids.

Jorpes¹¹ refers to the fact in his monograph on heparin, that the substance inhibits to some degree isoagglutination of red blood cells and that it has some effect or action in immunization processes. He has also stated that the effect of heparin is not longer than three to six hours, when given by single intravenous injection; and that it can be immediately counteracted by intravenous protamine sulfate or by transfusion. It is known that when the drug is given by slow intravenous drip, the duration of its action is for only thirty to sixty minutes after the infusion is stopped. Barnes and Erwin¹² have demonstrated that blood loss in the puerperium is not increased by the administration of heparin or dicumarol. These facts led us to conclude that the administration of heparin in pregnancy complicated by toxemia should be an innocuous procedure if used with reasonable care.

One of us (H. Z.) had gained considerable experience in the use of heparin in the treatment of deep thrombosis of the lower extremities¹³ and, in addition, had for some time considered its use in some of the systemic diseases involving thrombi in small vessels and capillaries. The anticoagulant action of this substance (heparin), as well as its reported (Jorpes¹¹) and apparent (J. M.¹⁴) ability to inhibit agglutination, led us to believe that it might have an effect in preventing the progressive changes in toxemia of pregnancy. With this in mind, a pre-eclamptic patient was treated by one of us (J. M.) at Woman's Hospital. The case history follows:

J. B. (No. 92,903), a 33-year-old unmarried primigravida was first admitted Feb. 22, 1947, as an emergency because of vaginal bleeding of 36 hours, marked edema, headache, and drowsiness for several weeks. She had had no medical care for eight weeks and only irregularly prior to that. Early in her pregnancy she was told that "all was well," but eight weeks prior to admission, her doctor, in another city, told her "complications were developing."

Past history: The last menstrual period was believed to have been in August, 1946. The menstrual history was otherwise normal. A review of the medical and surgical history contributed no pertinent information. There was no apparent evidence of previous hepatorenal disease.

Physical examination found a short, stocky female, edematous, drowsy, and obviously sick. The skin was moist and clammy, and there was marked pitting edema of the hands, feet, and sacral area. The ocular fundi presented no apparent abnormalities, nor did the heart and lungs. The blood pressure was 184/90, pulse 100, and temperature 98.8° F. The gravid uterus was estimated to contain a pregnancy of twenty-five to twenty-eight weeks gestation. The fetal heart was strong in the left lower quadrant. Vaginal examination showed the cervix closed, moderately eroded, and thick, and the presenting part to be high and to the left. The remainder of the examination was essentially normal.

Laboratory investigation showed the urine concentrated. A catheterized specimen contained 4 albumin, "nearly solid," and an occasional leucocyte. The hemoglobin was 10.5 Gm. with 3.89 million red blood cells per cubic millimeter. The leucocyte count was 5,680 per cubic millimeter, and the differential smear was normal. Urea nitrogen, the morning after admission, was 15.5

pressure fell to 160/110 but then during six days steadily rose to 190/120. At this time she was given 400 mg. of heparin daily for two days with a resultant fall in blood pressure to 145/?. The drug was discontinued at this time and again the pressure rose to 180/110 in a period of about 24 hours. Upon readministration of heparin the tension in less than 48 hours fell to 130/90 or less and there remained until her discharge. The urinary output which was about 250 c.c. daily decreased to 90 c.c. on the sixth hospital day, when heparin was first administered. It then increased to 585 c.c. two days later and to 1,300 c.c. five days later. The intake during this time remained approximately 600 c.c.

The two other cases in which heparin was used show some evidence of beneficial effect, however, the results are equivocal because its use was limited to the first few days post partum. During this time both patients showed gradual improvement not unlike that which would be expected in any untreated case following delivery.

Discussion

The striking results obtained by the use of heparin in the above-described case and the results similarly obtained in Finland prompted this rather premature report.

It would seem that this case (J. B.) presented on the first admission laboratory and clinical evidence of pre-eclampsia. Its course under the usual therapy was gradual improvement, but albuminuria and hypertension rapidly recurred in the clinic. Similar findings, but with a much larger amount of albumin, were observed on the second admission.

It appears rather remarkable that following the use of heparin the urinary albumin fell from 1.6 Gm. to less than 0.1 Gm. per liter nine hours after treatment. In addition, there was diminution and gradual clearing of the cellular elements. Concomitantly, the blood pressure dropped to 140/84 or less and there remained except for two elevations on the eighth and tenth days. Even more important was the definite subjective improvement. Accurate intake and output records were not charted. In general, however, the urinary output was greater during the second admission than in the first few days of the first admission.

It is granted that bed rest alone will frequently lower blood pressure and albuminuria to some extent. However, toxemia is a progressive disease, and spontaneous cures are rare, provided the pregnancy is maintained. From the first admission the clinical course of the case presented is witness of this fact. Following heparin therapy, toxic signs and symptoms failed to return to any significant degree. It is believed that, had heparin been used repeatedly, even greater improvement would have been manifest. The results obtained in Finland certainly suggest that heparin had a very definite effect on the postpartum eclamptic status of one patient, as manifest by the concomitant drop in blood pressure and the rapid increase in urinary output after heparin was administered. The clinician who treated this one patient has informed us that prior to the use of heparin he was certain this patient would not survive.

Since these patients were observed, the work of Odell et al. has been brought to our attention, and we believe that their results further substantiate our rationale for treatment. The recently published investigations of Schneider¹⁵ are of great interest. He has found that a toxic substance extracted from

evening of admission and the following morning, respectively. At 9 P.M. on the evening of admission, a continuous intravenous infusion containing heparin in distilled water and 5 per cent dextrose was started. This was discontinued at 1:30 A.M., April 1, 1947, because of impending labor, and after 150 mg. of heparin had been given. The clotting time which was normal prior to heparin was eighteen minutes by the Lee-White method when the drug was discontinued.

Following this treatment, the patient showed definite subjective and objective improvement. A catheterized urine the morning following admission showed only a trace of albumin which could not be measured. Subsequent analyses were similarly of small amounts, and in general remained substantially less than on the first admission. The drop in blood pressure is graphically shown (Fig. 1),

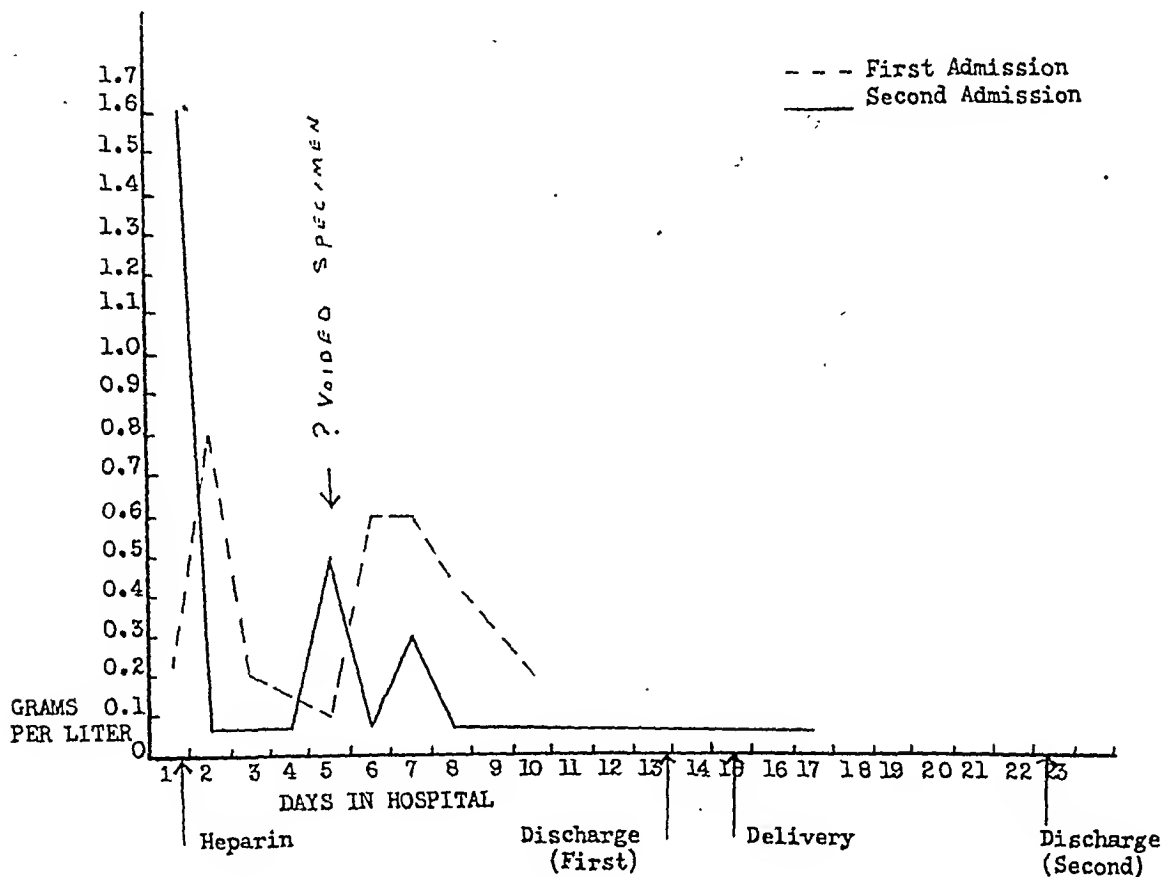


Fig. 2.

as is the urinary albumin (Fig. 2). It was noted that the blood pressure fell to less than 140/84 on the second day of hospitalization and, except for an occasional elevation, remained there or below. An episode of vertigo on the ninth day was associated with a dramatic, though temporary, drop in pressure. Progress continued satisfactorily except for some occasional unexplained nausea.

On the thirteenth day after an uneventful labor, she was delivered of a living infant weighing 1,616 Gm. Presentation was that of frank breech, and delivery was uncomplicated. The infant has made steady progress.

We have, in addition to the above case history, reports of three cases of toxemia of pregnancy treated in the University Obstetrical Clinic in Helsinki, Finland, under the direction of one of us (H. Z.). The records recently made available to us show that one of these, a 35-year-old primipara, was admitted with convulsions, a large amount of albumin in the urine, and a systolic blood pressure over 200. After four convulsions and death of the fetus, she was delivered per vagina by craniotomy and extraction. Following delivery the blood

PREGNANCY AND MULTIPLE SCLEROSIS

LOUIS H. DOUGLASS, M.D., AND C. LOUIS JORGENSEN, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, University of Maryland, School of Medicine)

MULTIPLE sclerosis as an entity has been studied quite exhaustively, and many articles about this condition have been published over the years. However, there appears to be a dearth of information about its course when complicated by pregnancy. A splendid review of the literature by C. H. Peekham appeared in the *New York State Journal of Medicine* 45: 618, 1945. The author recounted the number of cases found in the literature of foreign countries and mentioned how little has been written in our own country on multiple sclerosis and pregnancy.

Little we can say about the etiology of multiple sclerosis, its signs and symptoms, etc., could add to that already known, but Peekham asks the question: "What effect, if any, does multiple sclerosis have on pregnancy, labor, and the puerperium?" Also, he makes a plea that reports of cases of multiple sclerosis complicated by pregnancy should be made in order to increase our knowledge of the relationship between the two conditions.

Since 1939, there have been seen at the University Hospital in Baltimore, Maryland, five cases of multiple sclerosis associated with pregnancy; one in 1939, two in 1943, and two in 1946. A brief résumé of the cases and their treatment follows:

Case Reports

CASE 1.—M. H. The patient, a 34-year-old white woman, was first observed in the hospital in January, 1937. Her chief complaint was difficulty in walking, with weakness of both ankles. She stated that the onset of the condition dated back to 1934 when she "sprained" her right ankle. Since then, the patient has been unable to flex the right foot and noted some foot drop. She had to "pick up" and "put down" her right foot. Physical examination revealed a complete paralysis of dorso flexion on both sides (feet and legs). Inversion and eversion of right foot impossible with the two factors greatly reduced on the left. Peroneal muscles of both sides atrophied as well as the intrinsic muscles of the feet. Laboratory work was as follows: red blood cells, 3,900,000; white blood cells, 5,420; hemoglobin, 88 per cent; serologic test for syphilis was negative. Spinal tap revealed clear fluid with pressure of 100 mm. of H₂O; Quakenstead—negative; Wassermann and mastix tests—negative; cell count—negative for white blood cells, showing a trace of globulin. Her family and past histories were noncontributory, and past obstetric history revealed one abortion (year not obtained). The patient was discharged after six days' hospitalization, and was followed routinely on the outside. She was readmitted to the hospital on Jan. 1, 1939, at term, having gone through a prenatal period which was essentially negative. The multiple sclerosis was not aggravated by her pregnancy, and the findings were essentially the same as when she was first seen. Following fourteen hours of not too severe labor, she delivered a full-term living child weighing 6 pounds 8 ounces. Her postpartum course was uneventful, with no exacerbation of her condition.

placental tissue causes fatal multiple thrombi in mice when injected intravenously. The lesions in the liver of these experimental animals closely resemble the periportal necrosis of eclampsia. He concludes that this toxic substance is thromboplastin. It is known that the antieoagulant action of heparin is in part through its ability to neutralize thromboplastin.

Summary and Conclusions

1. Evidence from the literature has been presented to show that in pregnancy, and especially so in toxemia of pregnancy, at least one substance (fibrinogen) and possibly a second (thromboplastin) is present in increased amounts, and that in eclampsia the coagulation time of the blood is decreased, thereby predisposing to generalized diffuse thrombi.

2. It is believed that multiple, diffuse thrombi in small vessels associated with agglutination of red blood cells, particularly in parenchymatous organs, are instrumental in the clinical course of toxemia of pregnancy.

3. It is logical to assume that heparin, in part because of its antieoagulant action through its ability to neutralize thromboplastin and fibrinogen (?), and because of its antiagglutination effect, can inhibit the pathologic changes and favorably influence the clinical and laboratory findings.

4. A case of toxemia of pregnancy has been presented wherein two admissions, twenty-four days apart, were observed. During routine treatment on the first admission, gradual improvement was noted, but was followed by a return in force of symptoms after discharge. Abrupt and marked improvement which continued was observed nine hours after treatment with 150 mg. of intravenous heparin at a subsequent admission.

5. Three additional cases of toxemia treated in Finland have been mentioned. One of these, a severe toxemia with eclampsia continuing post partum, showed marked improvement after heparin therapy at a time when the prognosis was exceedingly grave.

6. Investigation is in progress to further establish the effect of heparin in this disease.

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Her first pregnancy was in 1931. She delivered a full-term living child which was normal in all respects following an uneventful prenatal course. Three months following delivery, she developed a sudden complete blindness of her right eye. This lasted three to four days, but gradually cleared up. There were no other signs or symptoms. Her second pregnancy in 1933 was uneventful so far as her prenatal course, labor, and puerperium were concerned. However, one month following delivery, she developed a painful nearly complete blindness of her left eye. This blindness continued for about five days, with a gradual abating of the condition. Her third pregnancy in 1936 was uneventful and, again, there was the onset of pain with associated blindness of her right eye. This slowly cleared, but the patient remained below "par" physically and began complaining of numbness of her legs. In 1942, the patient had a recurrence of left eye blindness which lasted for one week. This was followed by weakness and numbness of both legs. She was hospitalized for four weeks because she was unable to walk without falling, and was handicapped by the unilateral blindness. While in the hospital, she was treated with vitamin B complex with little relief of pain or symptoms. At this time, a diagnosis of multiple sclerosis was made.

She was again admitted to the hospital on June 7, 1943, ambulatory, eight weeks pregnant, and for a therapeutic abortion and sterilization. Physical examination revealed weakness of the muscle groups of the lower extremities; no ataxia, no nystagmus, and all reflexes normal save for the absence of the abdominals and a positive Babinski of both feet. No eye studies were done. The pregnancy was interrupted by an abdominal hysterotomy followed by sterilization by the Pomeroy method. Postoperative course was uneventful, and she was discharged after thirteen days' hospitalization in satisfactory condition.

This patient has not been seen since her discharge from the hospital, and further information about her condition is not available.

CASE 4.—A. O. This patient, a 31-year-old white para 0-0-1-0 was admitted to the hospital on May 28, 1946, with a history of multiple sclerosis of some twelve years' duration. She was admitted for study and treatment. She was in her sixth week of pregnancy; her last menstrual period had been April 11, 1946, and her estimated date of confinement was Jan. 18, 1947. In February, 1934, she noticed that she was beginning to drag her left foot when walking. The condition became progressively worse, and in May, 1934, while out walking, she fell to the ground, got up, and fell again. She was unable to stand on her feet without falling. She lost confidence in herself and didn't make an attempt to walk for fear she would lose her balance and fall. She was treated from 1934 to 1937 by "needles" and, in 1937, began taking sodium thiosulfate intravenously. She continued to lose ground, lost the feeling in her left leg, and the leg became numb. She continued treatment with sodium thiosulfate until 1938 with little improvement in her signs and symptoms, so finally discontinued the drug. The only sickness was scarlet fever in childhood without complications. The patient was admitted to a hospital in 1941 for a therapeutic abortion because of her condition. Otherwise, the obstetric history was negative. The previous pregnancy didn't seem to aggravate her multiple sclerosis.

Physical examination on admission revealed an unsustained lateral nystagmus of the left eye. There was marked spasticity of the lower extremities with diminished muscular power. Also, there was a moderate amount of intention tremor. All the reflexes were increased and hyperactive, abdominals were absent, there was a loss of vibratory sense in the lower extremities, marked ataxia, and marked spasticity of the lower extremities. She could not walk without assistance. Laboratory findings were essentially negative, and the serologic test for syphilis was also negative. She was discharged after one week's

Patient has been seen several times since 1939 and her condition remains unchanged. There has been no noticeable advance of the disease except for some increase in generalized weakness. There have been no other pregnancies or abortions and when last seen in April, 1946, her condition was satisfactory.

CASE 2.—E. H. The patient, a 23-year-old colored para 1-0-0-1 was first seen in the accident room on November 8, 1940, because of disturbance of gait of some 18 months' duration. Her history dated back to March, 1939, when, while out walking, she suddenly fell to the ground. She attempted to get up but her legs were so weak that any attempt to do so resulted in a recurrence of falling. She consulted her family physician who examined her, but could find nothing wrong. Three months later, in June, 1939, she lost control of her bowels and bladder. There was, however, a gradual return of these two functions. She began to have a feeling of "drawing up" of her arms along with some difficulty in walking. No pain or paresthesias were present. She was afraid to try to walk alone for fear she would fall.

Physical examination on admission revealed a well-nourished and well-developed Negro female whose only complaint was that mentioned above. A neurological examination revealed good muscular power throughout; there was a bilateral ankle clonus and Babinski; hyperactive knee jerks and ankle jerks; reflexes of upper extremities were good; loss of muscle tone and sense in lower extremities associated with a coarse intention tremor; abdominal reflexes not obtained; no nystagmus or scanning speech; gait was spastic, uncertain, and jerky, and she walked with a broad base. Laboratory work as follows: hemoglobin, 70 per cent; red blood cells, 3,900,000; white blood cells, 6500; serologic test for syphilis was negative; spinal tap, negative. She was observed in the hospital for ten days and was discharged in the same condition as on admission, and with a diagnosis of multiple sclerosis.

The patient was seen in the obstetric clinic on Sept. 14, 1945, for the first time. At this time, she was seven weeks pregnant, blood pressure was 132/88, weight was 110 pounds, and was apparently in satisfactory condition. She had had a full-term child in 1933, the prenatal course being complicated by a mild case of pre-eclampsia. On Feb. 15, 1946, the patient was admitted to the hospital for a check on her condition. At this time, examination revealed pupils which were unequal, and there was a suggestion of unsustained nystagmus of both eyes. There was moderate weakness of all muscle groups of her legs which was associated with a bilateral sustained ankle clonus—the latter more pronounced on the left. Abdominal reflexes were absent; Babinski, positive, bilateral; Romberg, strongly positive; and the heel to knee test was done very poorly. Her gait was ataxic. It was the opinion of the medical consultant that her condition was not any worse than when she was seen in 1940.

After an essentially normal prenatal course, and after fourteen hours of labor, she delivered a full-term child weighing 6 pounds $3\frac{1}{4}$ ounces by low forceps following central episiotomy. Her labor and puerperium were normal, and there was no exacerbation of her multiple sclerosis. Sterilization was recommended following delivery, which was refused.

This patient was seen one year following delivery. She stated: "The only thing I notice is a tendency to drag my left leg a little which was not noticeable before." Otherwise, her condition was quite satisfactory. There have been no subsequent pregnancies.

CASE 3.—E. C. This patient, a 30-year-old white para 3-0-0-3 was admitted to the hospital on June 7, 1943, because of multiple sclerosis, and with the strong recommendation of the referring physician that pregnancy be interrupted. Her past obstetric history is interesting, and is presented in detail for it brings out the reason why she was admitted.

Of the five, one, Case 3, was interrupted in our own clinic, and one, Case 4, elsewhere, although we felt that it should not have been done. Unfortunately, we do not have any recent information on the first of these two cases, and cannot say what her condition is at present. When she was first seen in 1939, our views on multiple sclerosis and pregnancy were still somewhat dependent upon those of the internist and neurologist, and it was more or less upon the recommendation of the consultants in these fields that the decision was made to interrupt the pregnancy. In the light of the present knowledge and belief of medical men and obstetricians, it is possible that pregnancy would have been allowed to continue in this case, although she did have a very bad history.

The other three cases would seem to warrant the conclusion, if we can draw one from such a small number of cases, that pregnancy has little, if any, effect on multiple sclerosis. The disease is one which is progressive and one in which remissions and exacerbations normally occur. It does not appear that the progress is accelerated by pregnancy, nor is pregnancy likely to cause exacerbations.

In these three cases, pregnancy proceeded more or less normally; there were no major obstetric complications, and labor was without special incident. All these infants were born alive and in good condition and did well. The puerperium was normal and uneventful.

From this, we can conclude that multiple sclerosis has no ill-effects upon pregnancy or upon offspring. It is our feeling at present that multiple sclerosis is not an indication for therapeutic abortion. There may be exceptions to this in individual cases where the disease is particularly severe. On the other hand, any woman afflicted with a condition as serious and as hopeless as multiple sclerosis appears to be at present, is probably better off if she is not burdened with a home and a family. The advice to remain single is good advice. If this is disregarded, perhaps contraceptives of one kind or another should be prescribed. Sterilization is only one method of carrying out contraception.

hospitalization, the decision having been made to allow her to continue with her pregnancy in that it was felt that the condition wouldn't be aggravated. However, one month later, the patient sought other medical advice and, without consulting us, was again hospitalized and aborted. The patient refused sterilization.

CASE 5.—T. I. This patient, a 24-year-old white para 1-0-0-1, was first seen in the hospital April 25, 1946. The first symptom, loss of vision following an attack of German measles, had its onset in February, 1945. She sought medical attention and was given a complete systemic checkup. Notation was made that the patient was quite unaware that she was dragging her right leg or that she was unsteady on her feet. She only complained of her left eye. Examination of the eyes revealed definite optic atrophy, a slow nystagmus on looking to either side, but more on looking toward the left. Neurological examination revealed a moderate Romberg response. The patient was awkward on her feet with eyes open. Pronation-supination test was poorly done with the arms. Deep reflexes were overactive in arms and legs, more marked on the right than the left, bilateral Hoffman reflexes, and a right Babinski. Laboratory work was essentially normal. Spinal tap revealed a Pandy of 3 plus; a colloidal mastie test of 4-4-3-2-2-1-0-0-0-0 which was stated as being highly suspicious of multiple sclerosis.

On admission to the hospital, she was in her first trimester of pregnancy—her last menstrual period had been Jan. 28, 1946, and estimated date of confinement, Nov. 5, 1946. The duration of pregnancy was approximately twelve weeks. The patient was admitted for study and treatment. There was no appreciable change in her condition since last seen. Her reflexes were as they were previously, and her ataxic condition was the same. She was discharged after fourteen days' hospitalization, with the decision to allow her pregnancy to continue.

Her first child, a full-term living baby born in 1941 without complications, was normal and healthy.

Her prenatal course was uneventful. There was no aggravation of her condition, and her pregnancy progressed uneventfully to term. She was delivered by central episiotomy and low forceps of a full-term living child weighing 6 pounds 8 ounces after three hours and forty-eight minutes of relatively mild labor—mostly back pains—on Nov. 7, 1946. Twenty-four hours post partum, she was taken to the operating room, where a routine Pomeroy sterilization was performed. Both the delivery and sterilization were done under spinal anesthesia. The Department of Neurosurgery was consulted, and they advised us there was no contraindication to using it in this case.

The patient has been seen on several occasions since delivery; she was last seen on Feb. 12, 1947. There has been no apparent exacerbation of her condition, and it can be said that her multiple sclerosis was not aggravated by her pregnancy.

Discussion

Above are the fairly complete records of five patients suffering from multiple sclerosis in whom the disease was complicated by pregnancy. Having studied these cases, what conclusion can be drawn? Are we any closer to an answer to Peekham's two questions as to the effect of pregnancy upon this disease and of the disease upon pregnancy, labor, and the puerperium?

These cases extend over a period of seven years from 1939 to 1946, and were treated by various physicians, although, more or less under the same general supervision.

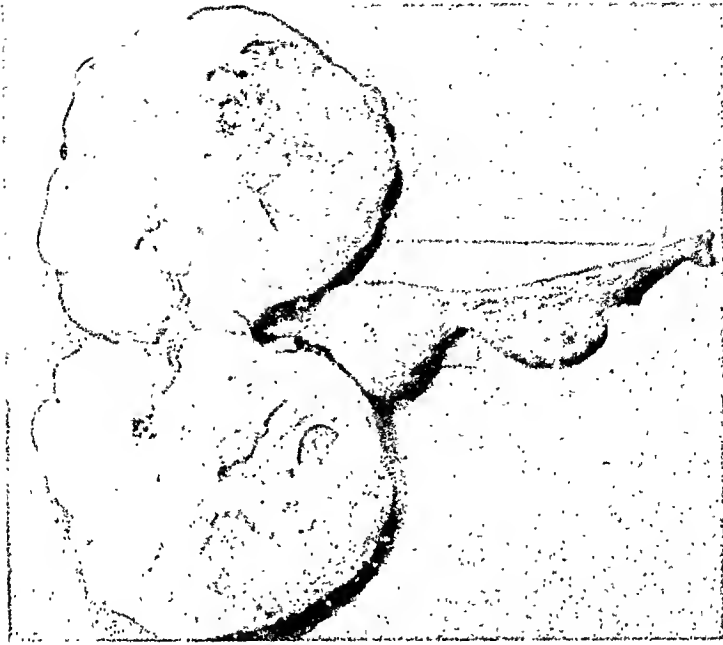


Fig. 1.—Operative specimen. (See text.)



Fig. 2.—(×100.) Photomicrograph shows clusters of round or ovoid cells arranged in alveoli and separated by a hyalinized connective tissue stroma which is infiltrated with an occasional lymphocyte.

DYSGERMINOMA OF THE OVARY*

BENJAMIN KAREN, M.D., AND J. IRVING KUSHNER, M.D., F.A.C.S.,
NEW YORK, N. Y.

(From the Gynecological Service and the Department of Pathology the Bronx Hospital)

D. S. HOSPITAL No. 186422. A female, aged 26 years, was first seen on Jan. 1, 1947, complaining of pain in right lower quadrant of four days' duration. The pain started while bowling. The past history was irrelevant. Menses started at the age of 12 years, were of the twenty-eight-day type, with a four-day flow. Her last period was Dec. 24, 1946. She had been married four years and there were no pregnancies, despite normal sexual relationships.

Examination revealed a well-developed white female about 120 pounds in weight. Her blood pressure was 120/80. The heart, lungs, head, and neck were normal. There was a slight bulging of the lower abdomen with a palpable, irregular mass occupying the entire left lower quadrant. Vaginal examination showed normal external genitals and a firm introitus. The cervix was small and pointed posteriorly. A hard, irregular, fixed mass involved the entire left adnexa and extended to the left anterior superior spine. The uterus was not palpable, although a line of cleavage could be ascertained between the body of the uterus and the adnexal mass. The right adnexa showed a tender palpable ovary.

On Jan. 14, 1947, under spinal anesthesia, operation was performed through midline suprapubic incision. A moderate amount of clear fluid was found in the peritoneal cavity. The left adnexa was found to be the seat of a large, irregular, nodular solid mass. The uterus was small. The right ovary was enlarged and cystic, with its attached Fallopian tube kinked. A supravaginal hysterectomy and bilateral salpingo-oöphorectomy was done. The patient made an uneventful recovery.

The specimen received in the laboratory was a uterus measuring 4 by 4 cm. in size removed supracervically with both tubes and ovaries attached. The serosal surface of the uterus was smooth and pink. The myometrium measured 2 cm. in thickness. The endometrium was pale and smooth. One tube measured 11 cm. in length and showed no gross pathology. The attached ovary measured 4 by 2 cm. in size, and on section revealed a 1 cm. lutein cyst and several smaller cysts. The other tube measured 4 cm. in length and showed no gross pathology. Its attached ovary measured 14 by 11 cm. The external surface was pinkish-yellow and was studded with numerous nodules of varying size. The capsule was apparently intact. On section a small amount of slightly turbid serosanguineous fluid escaped. Most of the ovary was firm, yellowish-white, and homogeneous. There were several irregular cystic areas interspersed, and the tissue was soft and hemorrhagic in the vicinity of the cysts. The nodules on the surface of the ovary were apparently due mainly to the lobulation of the mass. However, there were several nodules which were bright yellow in color and well demarcated from the remainder of the tumor (Fig. 1).

*Presented, in part, at a meeting of The Bronx Hospital Clinical Society on Mar. 3, 1947. Read at a meeting of The Bronx Gynecological and Obstetrical Society, Mar. 24, 1947.

PAROTITIS COMPLICATING THE EARLY PUERPERIUM

MERVIN W. GREENBERG, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics, Bronx Hospital)

THIS case is reported because of the rarity of its occurrence.¹⁻⁴ In the last ten years, among more than 26,000 deliveries at The Bronx Hospital, there occurred only one case of parotitis complicating the puerperium and one case of parotitis associated with pregnancy. The latter was a three and one-half months' spontaneous abortion in which swelling of the right parotid developed three days following passage of the products of conception. This was diagnosed as of the epidemic variety.

R. H., No. 186744, a 26-year-old gravida ii, para i, stated that she never had "mumps." However, following her first delivery on Sept. 15, 1944, on the eighth postpartum day, she developed swellings in front of both ears which lasted several days. This was not accompanied by temperature elevation.

In this delivery, the prenatal course was complicated by a slight but persistent albuminuria. The blood pressure was always low, varying only between 98/50 to 92/60. At no time did the patient exhibit edema or an excessive gain in weight; she was 151 pounds on Jan. 16, 1947. The Kahn and Wassermann reactions taken Oct. 17, 1946, were both negative, and the Rh factor was positive. Dental examination revealed caries of the upper and lower third right molars and the lower left third molar.

On Jan. 20, 1947, the patient was delivered of a living 7 pound 6 ounce male baby spontaneously, following a ten-hour labor. There was a first degree laceration which was repaired. The placenta and membranes were delivered and were complete and intact following a five-minute third stage.

During the first five postpartum days, the patient's temperature did not rise above 98.6° F. On the evening of the sixth day, the temperature rose to 101.6° F. Examination at this time showed that the pharynx was reddened, and glands were felt at the angles of both jaws. Except for these findings, the physical examination was negative.

On the following day, the temperature reached 103° F., with a slight acceleration of the pulse to 102. There could now be noted diffuse enlargement of both parotids. They had a rubbery hard consistency, but were only slightly tender. Each gland extended from the preauricular region to the angle of the jaw. The pharynx was clear. There was slight pouting of the opening of Stenson's duct, but no marked redness existed. The patient had very few subjective symptoms, and did not exhibit any discomfort upon chewing and swallowing foods, including even the very sour fruits.

Examination of the blood on the seventh day post partum at the height of the swelling showed 4,120,000 red blood cells, with 11.9 Gm. hemoglobin, 4,700 white blood cells, with a differential count of 69 per cent neutrophils, 14 per cent band forms, and 17 per cent lymphocytes.

On January 28, the eighth day post partum, the temperature reached 100.6° F. The left parotid gland had begun to decrease in size. The white-cell count on this day was 6,000, with 55 per cent neutrophils, 16 per cent band forms, and 29 per cent lymphocytes.

On the following day, the temperature was 99.6° F. The right submaxillary gland was now palpable and enlarged. However, the lymph glands were no longer palpable.

On January 30, the patient was seen by a diagnostician from the Department of Health, and the clinical diagnosis of parotitis was concurred, but the type was not definitely interpreted. It was advised, however, that isolation which had been practiced should be continued.

Microscopically, sections of the uterine wall showed the glands to be fairly normal in size, shape, and distribution. They were in the follicular phase with a compact stroma. Sections of the ovary revealed clusters of round or ovoid cells with clear, acidophilic, sparse cytoplasm arranged in alveoli and separated by a hyalinized connective tissue stroma. There were large areas of necrosis present. Section of the other ovary revealed several follicle cysts, one of which was filled with acidophilic secretion. Several corpora albicantes were present. Sections of Fallopian tubes showed no essential pathologic changes (Fig. 2).

Diagnosis.—Dysgerminoma of the ovary.

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1100 GRAND CONCOURSE
1840 GRAND CONCOURSE

PAPILLOMA OF THE CERVIX UTERI IN PREGNANCY

ROLAND R. SURAN, M.D., AND PETER C. MEISTER, M.D., BUFFALO, N. Y.

(From the Edward J. Meyer Memorial Hospital and University of Buffalo School of Medicine)

IN 1945, Edmonson, Levi, Evans, and Horn¹ called attention to the occurrence of a rare squamous epithelial lesion on the cervix uteri in pregnancy. They described six instances of papillomatous proliferations of the cervix in pregnant women ranging in age from 17 to 22 years. The histologic changes seen in these lesions were divided into three groups: "(a) simple thickening of the epithelium; (b) greatly thickened, irregular epithelial units indiscriminately fused together with confluent tiny papillary stalks; (c) large papillomatous growths."

In reviewing the literature, Edmonson, Levi, Evans, and Horn¹ found several references to the lesion under discussion. Cullen² and Norris³ stated that condyloma may occur on the cervix in pregnancy. Mershon⁴ reported two cases of papilloma in patients both aged 22 years, and in the sixth week of pregnancy.* DeLee⁵ mentioned in his text that he had seen three instances of nodular hypertrophy of the cervix in pregnancy.

Besides those cited by Edmonson and associates, we have discovered in the literature several other cases of papillomatous proliferation of the cervix in pregnancy. Meyer⁷ reported two specimens, one of which he described as a pointed condyloma, and the other as a circumscribed papilloma in a 27-year-old woman who miscarried at four months. Molmle⁸ recorded in detail a papilloma of the cervix in a 31-year-old multipara who had a miscarriage during the fourth month of gestation. Treite¹⁰ added two cases, one a pointed condyloma found in a 27-year-old woman pregnant for nine months, and the other a circumscribed flat papilloma in an 18-year-old primigravida in the third month of pregnancy.

Because of the infrequency of reports of papillomatous lesions of the cervix uteri in pregnancy, we describe an additional case.

Case Report

CASE 1.—E. S., an 18-year-old Negro primipara, was first seen in the prenatal clinic of the Edward J. Meyer Memorial Hospital on June 19, 1946. Date of the last menstrual period was April 24, 1946. Expected date of confinement was Jan. 31, 1947. The patient had a scant leucorrhea. The prenatal record mentioned that the patient showed no evidence of gonorrheal infection. The Wassermann test taken on the first visit was reported as negative.

The patient was admitted to the hospital on Feb. 2, 1947, in active labor. Examination revealed a left occipitoanterior position. The blood pressure was 150/100. Urinalysis showed one plus albumin and one plus sugar, with negative findings in the sediment. The patient was delivered of an 8 pound 12 ounce male infant by episiotomy and low forceps. Duration of the labor was thirteen hours and forty-five minutes.

Immediately after the delivery of the fetus the cervix was pulled down and inspected. It appeared normal except for an area on the anterior lip. Here was seen a circular, white, edematous papule estimated about 1 cm. in diameter,

*One of these cases was included in the report of Edmonson et al

X-ray films taken of the parotid areas on January 31 showed no evidence of calcification. Serum amylase determination on the same date showed an increase to 83 mg./100 c.c. over the normal of 20 to 40 mg./100 c.c. No agglutinins were found in the heterophile antibody titer determination.

A specimen of the patient's blood was sent to the Department of Bacteriology and Immunology of Harvard Medical School, and they reported a complement fixation test with mumps antigen and the patient's serum. The titer of the serum for mumps was very low, being 1:32, which was interpreted as indicating the possibility of mumps infection in the past. Another serum specimen drawn February 24, fixed complement in the presence of mumps antigen to a titer of 1:512. This would seem to favor the existence of a recent infection with mumps.

By the thirteenth day post partum, all the glands had completely subsided, and the patient was discharged the following day.

Comment

The question arises whether this patient had mumps or was suffering from a nonspecific parotitis. In this case, there is no history of exposure to the epidemic type. The rapid disappearance of the glandular swellings, the absence of lymphocytosis, the relative absence of tenderness,⁵ and the history of similar glandular swellings during the previous puerperium all point to the nonspecific variety of parotitis even though the titer of one of the serum specimens in the complement fixation test with mumps antigen was high.

As regards the cause of nonspecific infections of the parotid glands, there are two generally accepted theories. One is the "pyemic" theory or the hematogenous infection and the other is the "ascending" or infection passing through Stenson's duct from the mouth.⁶ The method of infection in this case could not definitely be determined, but the absence of any pyemic manifestation and the presence of defective mouth hygiene and caries of the molar teeth probably with associated deep-seated dental infection must be considered as probable etiological factors for the salivary glandular enlargements.⁷

The treatment of this case avoided the use of specifics such as the sulfonamides or antibiotics and included merely symptomatic therapy and the improvement of the oral hygiene. No surgical intervention was necessary in view of the absence of fluctuation and the rapid disappearance of the glands.

Summary

1. A case of parotitis whose onset began in the early puerperium is presented.

2. The history is unusual in that parotid glandular swellings occurred at the same stage of puerperium during the patient's both pregnancies.

3. Evidence is presented which would indicate that the infection is nonspecific.

Acknowledgment is hereby given for the advice and cooperation of Dr. Meyer Rosensohn and the staffs of the Department of Obstetrics and the Department of Pathology.

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figures of the normal type were frequent. In some areas the superficial layers of the epithelium showed a slight to moderate focal infiltration of neutrophils. The superficial cells showed marked vacuolization. Parakeratosis was present in some areas and keratinization was minimal. In a few areas the stratified epithelial proliferation was related to the columnar cells of the underlying glands. The central stalk of the papillary processes was composed of a highly vascular connective tissue stroma. The small blood vessels and capillaries were distinctly hyperemic, and hemorrhage throughout the stroma was a prominent feature. There was slight edema, with infiltration of round cells, plasma cells, and a few neutrophils. A few cervical glands were present, one of which showed slight cystic dilatation. No decidual cells were noted. The diagnosis was squamous papilloma.

The patient's course following delivery was uneventful. She was discharged from the hospital on Feb. 13, 1947. Her last blood pressure was 128/82; urinalysis showed a negative albumin, two plus sugar, and 10 to 15 pus cells per high power field.

The patient was last seen at the postnatal clinic on March 14, 1947. Examination of the cervix revealed a parous external os. The anterior lip showed a small nodule, about 0.3 cm. in diameter and elevated about 0.2 cm., which was not in the same location as the original lesion. The nodule was excised, and in addition, biopsies were taken from the anterior and posterior cervical lips. Smears and cultures of the urethra and cervix did not show gonococci. Complement fixation test for gonorrheal infection was reported as negative.

Pathologic Report.—Microscopic examination of the small nodule on the anterior lip of the cervix showed slight inflammation, chiefly superficial, with infiltration of neutrophils and round cells, and edema. Hemosiderosis was present. No stratified epithelium was found in the specimen.

The small biopsy fragment of the anterior lip of the cervix, taken from the base of the previously removed papilloma, revealed injection of capillaries, edema, and slight infiltration of neutrophils, round cells, and plasma cells. The preserved epithelium, which was of the stratified and columnar type, was crushed. No invasion could be seen.

The biopsy from the posterior lip revealed slight inflammation with hemosiderosis. It was covered by columnar epithelium.

Discussion

That papillomatous lesions of the cervix under any circumstance are of rare occurrence is evident from the relatively few reports in the literature.^{4, 6, 7, 8, 10, 11}

In addition to its rarity, the papillomatous lesion in our case was of interest because of its association with pregnancy, and because of its gross appearance which stimulated the clinical impression of a possible malignant tumor. In our abstract of the literature, we have already referred to the occurrence of papillomatous lesions of various grades in pregnancy.⁴ There is still discussion on the etiologic and pathogenetic factors for these lesions. Meyer⁷ stated that pregnancy may play some part in the cause other than contributing an increased susceptibility to inflammation. Edmonson and associates⁴ suggested the hormones associated with pregnancy were determining factors. Hofbauer,⁵ who demonstrated proliferative changes in the cervical mucosa and glands during various stages of pregnancy, also mentioned hyperplasia of the portio epithelium. It was his belief that the anterior pituitary hormone might be responsible for both of these cervical changes.

Papilloma of the cervix has occasionally been reported in nonpregnant women, apparently on the basis of inflammation. Gonorrhea appears to be the

with multiple, minute, short papillary projections on the surface. The entire lesion was excised following the application of a suture ligature about the base, and submitted for pathologic examination to exclude malignant tumor.

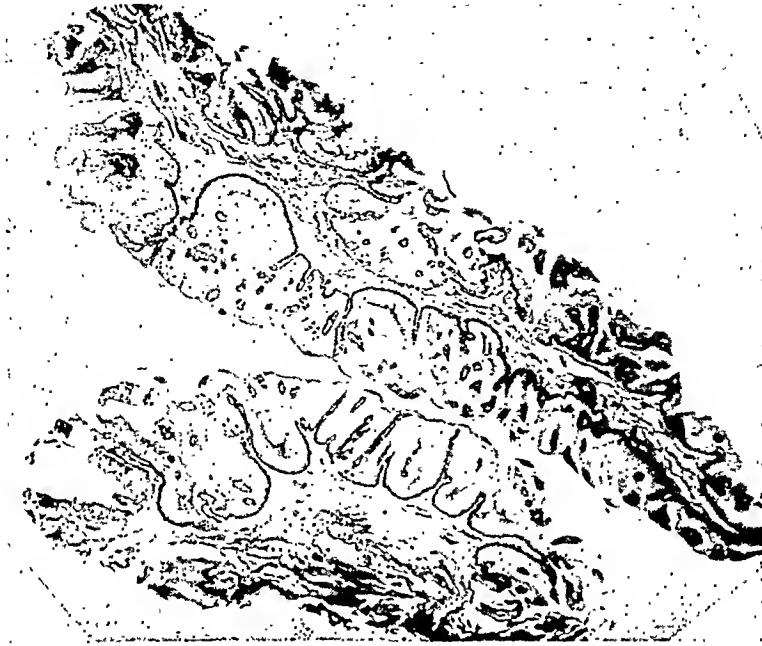


Fig. 1.—Low power view of the entire papilloma.

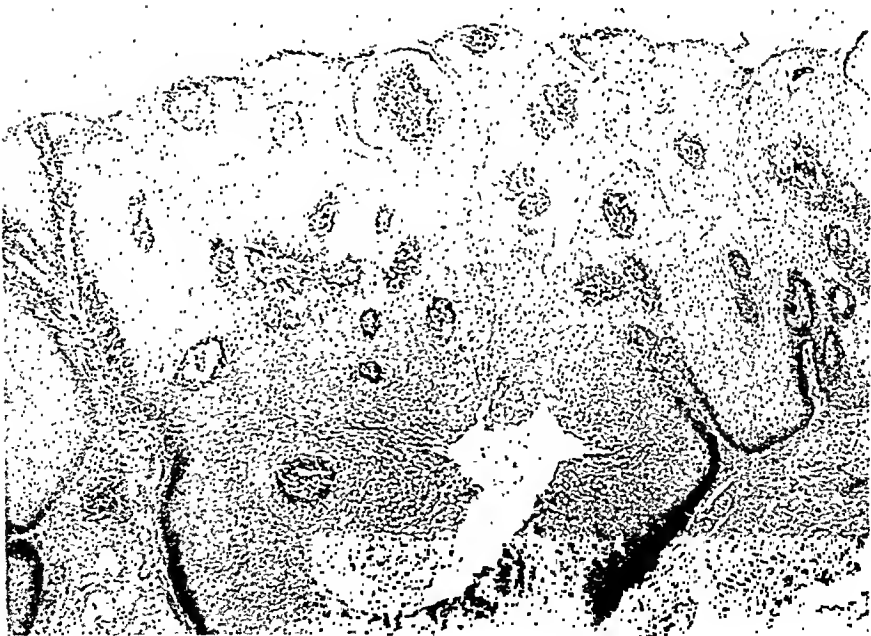


Fig. 2.—Epithelial appearance of the papilloma.

Pathologic Report.—Grossly, the biopsy specimen measured 2.5 by 1.2 by 0.4 cm. Microscopic examination of the cervical lesion revealed a papillomatous growth, with multiple, branching processes, covered by a distinctly thickened stratified squamous epithelium. The basement membrane was intact. The basal cells were large, with large nuclei, and appeared fairly uniform. Mitotic

A MODIFIED METHOD OF SURGICAL REPAIR FOR PROLAPSE OF CERVICAL STUMP WITH ASSOCIATED ENTEROCELE

DAVID ROSE, M.D., BOSTON, MASS.

(From the Mount Auburn Hospital.)

THE prolapse of a cervical stump following supravaginal hysterectomy is a distressing occurrence following abdominal removal of a uterus. The surgical repair is difficult in that attempts at repair per vaginam often are attended with partial or complete closure of the vagina, or, if the vagina is maintained as a functioning structure, the repair is often incomplete.

There have been many methods of repair advocated, ranging from removal of the cervix and ligamentous apposition and closure to fixation of the cervix to the pubis.

In the case herewith reported the patient was a 61-year-old multiparous white woman. Twelve years ago an abdominal supravaginal hysterectomy was performed at another hospital. About one year ago she noted a bulging in the vagina which became progressively worse. There was an associated frequency and some dysuria. Examination revealed an elderly woman in good general condition. Vaginal examination disclosed a large cystocele and prolapse of a cervix, with a small external os completely outside the vagina. Palpation revealed the cervix almost entirely absent, with only a vaginal cuff of cervix remaining. Posterior to the cervix was an enterocele about the size of a lime. There was a small rectocele. The patient was admitted to the hospital and operation subsequently performed.

Operation.—Under spinal anesthesia, an inverted T incision was made just above the external os and carried up to the urethra. The vaginal mucosa and its underlying fascia were bluntly dissected off the bladder and superiorly and laterally to the pubis, revealing the subpubic fascia. The bladder was then stripped off the remnants of cervix, which proved to be about one-half inch long, until the peritoneum was visible. The cross arm of the inverted T incision was extended posteriorly, completing the denudation of the cervical cuff. The cervix was then divided anteriorly, through the external os in a longitudinal direction up to the peritoneum. At the top of this incision, the cervix was split by a transverse incision through the anterior lip. The cervical cuff was thus transformed from a small cylinder to a flat rectangle. Since in this case there was no secreting endocervix, no denudation was necessary. If the endocervix is functioning, it should be removed. This flap was then sutured by interrupted white cotton sutures to the subpubic fascia, after the bladder had been pushed back into the pelvis above the pubis. The posterior vaginal mucosa which had been incised and freed from the cervix was then dissected further posteriorly. The uterosacral ligaments were palpable and sutured together without opening the peritoneum of the posterior cul-de-sac, and then sutured to the superior margin of the transposed cervical flap. The anterior vaginal flaps, which had not been trimmed off, were divested of the outer layer of mucosa by shaving a thin layer off with a scalpel. This shaving extended upward almost to the lateral edges of the pubis. The flaps were then divided so as to obtain two strips of tissue (one on the left and one on the right), about three-fourths inch wide, maintaining its integrity above. The right strip was then crossed over the transplanted cervical flap and sutured to the subpubic fascia. The same procedure

commonest offender, although tuberculosis is also a frequent cause. Other factors included are chronic discharge and mechanical stimuli from a pessary. Norris⁹ held that condylomas of the cervix in pregnancy were secondary to gonorrheal cervicitis. In our case, however, the clinical, bacteriologic, and histologic findings offer no convincing proof for an infectious cause.

The lesion in our case fell into the group of large papilloma, and the lesion, because of its gross appearance, raised the clinical suspicion of a malignant growth; histologically, though in active proliferation, it showed a benign character. It is interesting to note that several patients with papillomatous lesions of the cervix were treated with radium therapy, apparently on the suspicion of malignant tumor from the gross appearance,⁴ and that certain papillomatous lesions were originally considered malignant by pathologists after microscopic examination, later to be regarded as benign, only after review of the slides.⁷ Cattaneo¹ went so far as to write: "Papillomas of the portio, besides being rare, very rarely are benign in as much as often they are the precursor of a malignant epithelial tumor." He further added that they should be regarded in the same manner as polyps of the rectum and papillomas of the urinary bladder. On the other hand, Meyer,⁷ who classified papillomatous lesions into three types: (a) pointed condyloma, (b) flat diffuse papillary growths, and (c) circumscribed papilloma, stated that there was no evidence for considering the possibility of a malignant transformation in these lesions.

Summary

1. The literature on papilloma of the cervix uteri in pregnancy is briefly reviewed.
2. An additional case of papilloma of the cervix in pregnancy is reported in detail.
3. Papilloma of the cervix can be separated into two main groups: (a) inflammatory, (b) gestational. The etiology of each is briefly discussed.
4. The points of view on malignant transformation are presented.

The authors wish to express their thanks to Dr. Samuel Sanes for his kind assistance in the preparation of this article.

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Special Article

CURRENT TEACHING TRENDS IN OBSTETRICS*

JOSEPH L. BAER, M.D., CHICAGO, ILL.

THE first course in midwifery in the American colonies was given by Dr. William Shippen in Philadelphia in 1762. He, John Morgan, and Thomas Bond established the first medical school in the colonies in 1765 in Philadelphia under the auspices of the University of Pennsylvania.

It has taken the past fifty years to eliminate the diploma mills and unapproved schools. There is one still surviving in the United States.

The need to be approved by the Council on Medical Education and Hospitals for internships and residencies of the American Medical Association and the continuing surveys by the American Medical Association and the American College of Surgeons, has resulted in vast improvement in the quality of service rendered and instruction given in our hospitals. Credit is also due to the Association of American Medical Colleges. This is the framework in which young men and women have been and are being prepared for the practice of medicine and, more particularly, obstetrics. The ingredients for producing the kind of physician who can best serve the public are threefold: the caliber of the teachers, the quality of the students, and the availability of adequate teaching facilities at all levels of medical education.

The final factor in education is the teacher. This is the ingredient which will in the main determine the quality of our physicians. The objective of the real teacher must be to arouse and maintain interest, to stimulate independent thinking, to help develop powers of observation.

There are three types of research:—clinical; basic; that is, investigations in the allied sciences which have a clinical bearing; and abstract. Most well-run hospitals afford opportunities for clinical research. University hospitals, in addition, can support basic research in conjunction with the departments of the allied sciences. Abstract research has no place in a medical environment. Teachers certainly should have an understanding of the implications and potentialities of clinical and basic research.

I am firmly convinced that heads of medical school departments in our specialty certainly, and probably in all clinical specialties, should be seasoned clinicians who have a flair for teaching and an appreciation of research. Students, interns, residents, and junior members of the department are entitled to that kind of leadership.

The part-time professorship seems to be an ideal compromise between the full-time professorship and the clinical professorship. This is the most widely

*From the opening address before the American Congress on Obstetrics and Gynecology, September 8, 1947, St. Louis, Mo.

was then used, carrying the left strip to the right subpubic fascia. Thus was constructed crossed layers of denuded mucosa and fascia sutured to the subpubic fascia, in the fashion of sliding grafts, creating a sling under the transposed cervical flap. The excess vaginal mucosa was trimmed off and sutured together from below the urethra down to the point where the top of the plication of the uterosacral ligaments had been started. The posterior vaginal mucosa was then trimmed and sutured to the bottom edges of the anterior layer. A high perineal repair was then completed in the usual manner. Upon completion, the reconstructed vaginal tube admitted two fingers and extended about three inches in depth. A retention catheter was placed in the bladder and the patient returned to bed in good condition.

The postoperative convalescence was uneventful, and the patient was discharged home on the thirteenth postoperative day. Examination on discharge revealed a well-healed perineum. The vagina admitted two fingers. The anterior vaginal wall was healed, and there was no bulge on straining. A thick ridge could be felt under the symphysis pubis, and the vaginal canal was patent for about three inches. There was no bulging or relaxation at the dome of the vagina. Re-examination, six months later, revealed no change.

Summary

A typical case of prolapsed cervical stump with associated enterocele and cystocele following abdominal supravaginal hysterectomy is described. A modified method of repair utilizing sliding fascial-mucosal grafts and transposition of cervical flap is described.

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partment heads, or to include the privilege of private practice. This will attract the kind of leaders such departments should have.

The junior teachers can well be of two kinds, those with a clinical background and those with an interest in or a capacity for basic research. Here, too, salaries should be sufficiently attractive plus practice privileges to hold the better men. Thus all grades of students will be exposed to a properly balanced faculty under real leadership.

I am particularly concerned with this trend away from seasoned leadership on behalf of the thousands of established physicians who are being urged to take advantage of refresher courses and postgraduate instruction. Surely they have a right to expect that their teachers have been exposed to the problems which have confronted them.

I believe I have justified the thesis that the quality of leadership in our teaching institutions is of prime importance. The essential qualification among these leaders must always be adequate clinical experience for which there is no substitute.

avored plan at the present time. From the standpoint of the school it is more economical than the full-time professorship. It is less restrictive and more broadening in opportunities for the individual and generally more inviting to any capable man than either of the others. Under this plan, men may be attracted to come to a school from elsewhere if that is desired, or local men find it possible to discontinue the routine and relatively minor parts of their private work in order to give more time to the school.

In recent years the magic word "research" has become a shibboleth in medical schools and hospitals. Many, including trustees of schools and hospitals, have begun to regard it as the touchstone of qualification. Nothing could be further from the needs of the junior physicians and the women for whom they are to render care.

Research in all its ramifications is the foundation of progress. Laboratory research is primarily the province of the younger physicians who have the imagination and the leisure and should get their leads from their elders. Clinical research can be carried on throughout a lifetime clinical career.

Good teachers have certain characteristics. They enjoy teaching. They have the gift of stimulating and holding the interest of their students, and they have a broad personal knowledge of that which they are teaching.

In recent years some well-established schools and some new state medical schools, handicapped by limited resources and perhaps blinded by the radiance of the magic word "research," have selected department heads who still had their spurs to win on the battlefield of clinical practice. I believe this is an unkindness to such men and a gross injustice to their students, interns, residents, and staffs. Never forget that our keenest critics are those whom we undertake to teach.

However, the financial needs of the faculties of most of our medical schools, the teachers who must train the physicians of the future to care for the entire population in health and disease, continue to be neglected. Very few schools have an income and budget which enable them to compete for medical teachers against the lure of private practice. State university medical schools are steadily assuming a greater role in the training of physicians at all levels of development.

There are 70 approved medical schools in the United States. They have a combined active teaching faculty of 1,516. There are also 292 well-organized hospital maternity divisions with approved residencies. The department heads and chiefs in the obstetric divisions of these schools and hospitals do not change overnight. There are currently 2,395 Diplomates of the American Board of Obstetrics and Gynecology and, in addition, approximately 4,800 mature and well-qualified clinicians who have not seen fit to seek Board Certification. Surely, out of these two groups replacements can be found which will meet with general approval on the basis of experience and teaching ability.

Organized medicine, state medical societies, and school alumni associations should take on as one of their most urgent tasks a campaign to increase these state school budgets sufficiently to enable them to pay adequate salaries to de-

orally, but he is convinced that if they kept on, this nausea always disappears. He controls bleeding by means of 5 mg. of stilbestrol, by mouth, every fifteen minutes. In severe cases, he injects an oily solution of stilbestrol directly into the cervical tissue. According to Karnaky, 100 mg. of stilbestrol, taken in from 3 to 6 weeks, reduces polycystic ovaries to normal. Before hysterectomy he gives from 250 to 1,000 milligrams. In 4,134 endometrial biopsy specimens he found secretory endometrium in only 5 per cent of all women who suffer from excessive bleeding. These biopsies are done on the first day of the menses. In women under 35 years old, or where carcinoma is not suspected, he does office curettages for menorrhagia. After having performed 1,557 kymographic tracings, he believes that they are as accurate as endometrial biopsies for the determination of ovulation. However, as far as one can judge, he has no controls whatever to substantiate this assertion which in both tests rests more upon credulity than actual proof. Fifty consecutive patients have not aborted since stilbestrol was started, giving 10 mg. daily. When there is cramping or spotting, he gives 50 to 100 mg. every fifteen minutes. Another illustration of the author's heterodoxy is the fact that he considers the ordinary pregnancy test too time-consuming, and places much reliance on vaginal scrapings which, if they turn black with iodine, he considers a proof of pregnancy; also if 5, 10, or 25 mg. of stilbestrol do not cause vomiting or nausea, 90 per cent of these patients are pregnant; and finally, if the vaginal pH is between 3.5 to 3.9, it is further proof. I could continue giving instances covering the rest of the book, but this will give the reader a very good idea of what to expect. There is much that is stimulating, new and interesting, but a good deal of it has to be taken with several grains of salt.

The monograph is faultlessly presented, contains many good illustrations and a number of colored plates which to most readers will prove familiar, as they have been borrowed from the pharmaceutical advertisements with which physicians are showered. R. T. FRANK.

The second edition of Wharton's *Gynecology With a Section on Female Urology*³ has appeared. The first 760 pages deal with gynecology. The succeeding 240 pages are devoted to urology. Both sections go into details of each specialty. One can consider the presentation as that current at the Johns Hopkins Hospital, and still influenced to some degree by the methods of the late Howard Kelly. The text is clear and to the point. The exposition is conservative, but takes in all of the newer acquirements. The book is beautifully illustrated, largely based on pictures culled from the literature, which in this case are chosen with such care and intelligence that they show more than any single author ordinarily could present if he limited himself to his own collection.

I would suggest that among the pessaries to be described the Gellhorn receive attention and illustration, and even the old Schatz has its value. An unusually good chapter on the sympathetic nervous system is worth-while reading. I note with pleasure that in urology the water cystoscope is finally described, although previously the Johns Hopkins gynecologists have remained faithful to the Kelly air cystoscopy, which in my opinion has a much more limited application. Altogether the book is very satisfactory. R. T. FRANK.

*Functional Surgery in Gynecology*⁴ is a peculiar book. It covers the operative indications, the operative techniques, the physiological and physiologico-pathological aspects of endocrinology, on the whole, in a very satisfactory fashion. The strangeness of the book consists of the fact that it appears to have been written behind a Chinese wall. With the

³*Gynecology With a Section on Female Urology*. By Lawrence R. Wharton, Ph.B., M.D. Assistant Professor of Gynecology, The Johns Hopkins Medical School; Assistant Attending Gynecologist, The Johns Hopkins Hospital; Consultant in Gynecology, The Union Memorial Hospital, Hospital for the Women of Maryland, Sinai Hospital and Church Home and Infirmary. Second Edition. With 479 Illustrations. 1027 pages. W. B. Saunders Company. Philadelphia and London. 1947.

⁴*Chirurgie Fonctionnelle Gynécologique*. Indications opératoires, techniques et considérations pratiques en rapport avec les acquisitions endocrinologiques. R. Bourg, Chef du service universitaire de gynécologie à l'Hôpital Brugman, Bruxelles. Preface de E. Douay, Président de la Société Française de Gynécologie. Paris. 267 pages. Masson & Cie. Paris (VI^e). 1947.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

This Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears¹ by Gates and Warren appears in a very attractive form. Papanicolaou has written the foreword. It has been published with the help of the Massachusetts Division of the American Cancer Society. The technique is described in great detail. The main value of the book lies in its fifty beautiful plates covering every aspect of findings, including the normal ones. The text is short, and is really a commentary and elucidation of the plates.

No matter what one's opinion may be, this type of diagnostic investigation has come to stay. Even if some of its advocates and introducers are too sanguine, the method certainly has value.

When I see the data of Papanicolaou and Traut, of 7,000 to 10,000 smears with the percentage error of 0.3 per cent, only twelve false negatives and no false positives, I must express my doubts, because I have had several cases of positive smears taken by men who have had full experience in the technique, where subsequent curettage and biopsy as well as observation have shown that there was no neoplasm.

R. T. FRANK.

Practical Office Gynecology by Karnaky² is a very personal book containing a great deal of information and also a great many personal interpretations, some of which certainly will require revision. The purpose of the book is to describe the symptoms which may be elicited in the office and particularly treated medically, probably a revulsion against the "overzealous exercise of surgical judgment" which in plain English I interpret as "unnecessary surgery." The author emphasizes that uterine bleeding is controlled by changing the blood level of estrogens. This he does by means of diethylstilbestrol. He places great faith on diagnosis of the acid reaction in the vagina, ovulation determinations for sterility, particularly by the rectal temperature changes, and the endometrial biopsy method. The author is a great believer of the uses of stilbestrol which seems to be his cure for almost all the gynecologic ills to which women are subject. Of 3,982 patients given stilbestrol, 82 per cent experienced nausea and vomiting no matter whether the drug was prescribed parenterally or

¹A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears. By Olive Gates, M.D., Pathologist, Massachusetts State Tumor Diagnosis Service; Assistant Pathologist, Pondville Hospital (Massachusetts Department of Public Health); and Shields Warren, M.D., Assistant Professor of Pathology, Harvard Medical School; Pathologist, New England Deaconess and New England Baptist Hospitals; Reserve Consultant in Pathology to the Bureau of Medicine and Surgery, United States Navy, Captain (M.C.) U. S. N. R. With a foreword by George N. Papanicolaou, M.D., Ph.D., Associate Professor, Department of Anatomy; Research Associate, Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital. 182 pages. Harvard University Press, Cambridge, Mass. 1947.

²Practical Office Gynecology. By Karl John Karnaky, M.D., Assistant Professor of Clinical Gynecology, Baylor University College of Medicine; Gynecologist to Jefferson Davis Hospital, Houston, Texas; Director of Menstrual Disorder Clinic, Jefferson Davis Hospital; on Courtesy Staff of St. Joseph Infirmary, Memorial Hospital, Hermann Hospital, Heights Hospital, Park View Hospital and Methodist Hospital, Houston, Texas. 261 pages. Charles C Thomas, Springfield, Ill. 1947.

them in reprint form, bound with the main volume. Of particular interest are corpus carcinoma in infants, three cases of primary tubal carcinoma, and two cases of cervico-uterine fistulae.

R. T. FRANK.

Practical Obstetrics by Mayes⁸ comes from the far antipodes. The volume grew out of bulletins on obstetrics for wartime graduates in the services. Its main aim is to be practical, clinical, and is meant for young doctors going into practice. Its motto is "early diagnosis: late interference." The presentation is in the form of histories of actual cases as, for instance, in the beginning two cases of postpartum hemorrhage, a discussion of the forms of treatment to be considered, and then a description of these treatments, including manual removal of the placenta, the injection of pituitrin and ergot preparations, Crédé's extraction. Lovsett's technique of delivering the arm in breech presentations is advised. The manual rotations of occipitoposteriors is described, and if this is ineffectual, to pass the hand beyond the head, hooking the shoulders around. The description of forceps is limited to the axis traction instrument. Such procedures as episiotomy, lower segment cesarean, induction of labor, induction of therapeutic abortion, especially by hysterotomy, the treatment of sterility, artificial insemination are taken up; likewise a discussion of the Rh factor in pregnancy, rubella, and pregnancy. It is a well-designed book, profusely and well illustrated by drawings by Schiavo, and contains a number of colored plates in addition. The book should serve its purpose very well, particularly in isolated communities where the doctor is left entirely on his own.

R. T. FRANK.

Will and Agüero have published a handsome fascicle which they call **Obstetric Illustrations**,⁹ for the reason that they hope to continue these publications, and secondly that although the context is variegated and far from complete from many points of view, it represents the special cases culled from a large obstetric clinic where 6,000 patients are confined each year (Concepción Palacios). The text is very short, hardly more than explanatory to the beautiful, large sized lithographs (6½ by 8½ inches). They cover everything from a normal full-term uterus, with and after the fetus has been removed; rupture of the uterus; abdominal pregnancies; and then a number of unusual fetal deformities, gross and in gross section. This beginning of an atlas should prove of use, particularly where a large clinic material is not available. It is the first publication from Venezuela that we have had for a long time, and is therefore welcome because it shows that this part of South America is taking part in the wonderful strides in advancing medicine that South America is now showing.

R. T. FRANK.

Miscellaneous

Female Sex Endocrinology by Calatroni, Ruiz, and Di Paola¹⁰ is a large, profusely illustrated, and minutely documented monograph covering the subject in an unusually

⁸**Practical Obstetrics.** By Bruce T. Mayes, M.V.O., M.B., B.S. (Sydney), F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G.; Professor of Obstetrics, University of Sydney; Senior Honorary Obstetrician, King George V. Memorial Hospital for Mothers and Babies, Sydney; Honorary Obstetrician, Royal Hospital for Women, Sydney; Honorary Consulting Obstetrician, Women's Hospital, Crown Street, Sydney. Drawings by Vergil Lo Schiavo, B.A. (Sydney). Diploma Royal Academy (Rome and Florence). 306 pages. The Australasian Publishing Co. Pty. Ltd. Sydney, 1947.

⁹**Ilustraciones Obstetricas.** Por los Doctores Gerardo Will, Ex-adjunto del Instituto de Anatomía Patológica (Director: M. Ascanazy) de la Universidad de Ginebra.—Médico de la Casa Municipal de Maternidad "Concepción Palacios," Caracas.—Facultad de Medicina e Instructor de la cátedra de Histología Normal de la Universidad de Venezuela y Oscar Agüero, Médico-Partero, Adjunto del Servicio No. 2 de la Casa Municipal de Maternidad "Concepción Palacios," Caracas. Prólogo Por el Doctor: Leopoldo Aguerrevere, Profesor de Clínica Obstétrica de la Universidad Central de Venezuela. Casa Municipal de Maternidad "Concepción Palacios," Caracas. 1946. Editorial Grafolt. Caracas, Venezuela, 1947.

¹⁰**Endocrinología Sexual Femenina.** Carlos J. Calatroni, Docente libre de Clínica Ginecológica (Buenos Aires); Vincente Ruiz, Ex prof. titular de C. Ginecológica (La Plata) Jefe del Serv. de Ginecología del H. Español (Buenos Aires); Guillermo Di Paola, Docente libre de Clínica Ginecológica (Buenos Aires) Subjefe de Servicio del Hospital Rivadavia. Prólogo del profesor Dr. Bernardo A. Houssay. 724 pages. Librería Y Editorial "El Ateneo," Buenos Aires. 1947.

exception of five or six vague references to the literature, the only way of recognizing the fact that others have done work in gynecology is from the naming of a few operations with author's name such as the Alexander, the Pozzi, and the presacral resection of Leriche.

The author displays great faith in endometrial biopsy. He insists on the use of lipiodol in salpingographs and does not even mention the water soluble media. While the sulfonamides are mentioned, penicillin is not referred to. The book is well illustrated, contains a wealth of good material, and should be of great service particularly to the general surgeon who dabbles in gynecology and has not the time to keep abreast of the newer, particularly less radical procedures such as myomectomy, implantation of the tubes, resection of the ovaries, ovarian grafts, etc.

R. T. FRANK.

The 1946 Transactions of the American Society for the Study of Sterility⁵ contains a large amount of interesting material with good discussions. This rather small but apparently very active society based its first discussion on Methods of Increasing Fertility in Domestic Animals by M. G. Fincher, D.V.M., from the Veterinarian College of Cornell University. I am glad to see that physicians are again paying attention to the excellent work done by veterinarians who are able to control the material in a fashion impossible in human beings. An article of considerable value is that by Halford of Honolulu, based on Observations on Racial Fertility and Sterility in Hawaii where Hawaiians, part-Hawaiians, Puerto Ricans, Caucasians, Chinese, Japanese, Koreans, and Filipinos have lived in harmony for many years. The Effect of Prolapse of the Ovaries Upon Cystic Degeneration and Ovulation by Weed and Collins is far from convincing. Greulich has carefully studied the Reliability of "Basal" Body Temperature Changes as an Index of Ovulation in Women. His well-controlled experiments are a very good indication of ovulation and conception but, as he says, there is no reason to believe that the technique is infallible. X-ray Irradiation to Promote Ovulation is discussed by Haman. Rommer's discussion of Psychoneurogenic Causes of Sterility and Their Treatment, With Preliminary Remarks on Allergenic Sterility discusses a new field but is far from being completely convincing, although the author believes that there are definite psychogenic and neurogenic causes for sterility which act through "a hormone-sympathetic imbalance in the system"; an interesting secondary observation were the definite vaginal and cervical contractions demonstrated by intracervical and intrauterine graphs connected with a kymograph system during coitus. A number of other articles are of great interest but cannot be reviewed in detail.

R. T. FRANK.

A short monograph on Leucorrhea in the Females⁶ covers the subject in a rather detailed fashion. Particular attention is paid to *Trichomonas vaginalis*. The world literature is taken up in detail.

R. T. FRANK.

The twenty-first volume of the *Annales of the Obstetric and Gynecological Institute of Helsinki's University* appears under the editorship of Mauno Rauramo,⁷ to whom the volume is dedicated. It also includes the twenty-fifth volume, second supplement of *Acta Obstetricia et Gynecologica Scandinavica*. Fortunately for the reviewer, a great majority of the articles are written either in German, French, or English, or have summaries in these languages. The University Clinic sees close to 4,000 patients a year, in a ratio of 3 to 1, in obstetrics and gynecology. The first 100 pages are devoted to statistical tables. Then follow a large number of diverse articles covering both obstetrics and gynecology, some of

⁵1946 Transactions of the American Society for the Study of Sterility. Edited and published by The Western Journal of Surgery Publishing Company, Portland, Oregon. 174 pages.

⁶Flujos Genitales Femeninos. Dr. Alonso Restrepo. Trabajos de la Academia de Medicina de Medellin. Reproduccion de "Anales de la Academia de Medicina de Medellin"—III Epoca—Vol. III—No. 2—Julio, 1946.

⁷Annales Instituti Obstetrici et Gynecologici Universitatis Helsinkiensis. Edidit Mauno Rauramo. Tom. XXI, Anno MCMXLV.

Hormonal Aspects of Procreation¹³ is merely a part of his more ambitious publication just reviewed. The main theme is the assertion that the activator of the ovum is the gonadotropic hormone absorbed from the hypophysis.

R. T. FRANK.

The first monograph from Vienna since the war that has come into our hands is that by Dr. Gottfried Hartmann, who describes a very rare case which he calls **Osteophthsis of the Pelvis and Femur**.¹⁴ This female patient was watched for many years in the clinics of Vienna. The pelvic girdle became a soft tissue, as did the upper portion of the femur. She was twice delivered by cesarean section and finally died, permitting a full autopsy. Some aspects of the case were not studied, such as the blood chemistry, which after all would have been of supreme importance. The author, after giving the full history and autopsy reports of the patient, then reviews the various bone conditions which should be taken under consideration in diagnosis, including bone atrophies, aseptic necrosis, inflammatory conditions, parasites, Hand-Schüller-Christian disease, primary and metastatic bone neoplasms. The monograph is illustrated with a number of x-ray pictures of the patient's bones.

R. T. FRANK.

The first edition of **Diseases of Metabolism**, edited by Garfield G. Duncan, was reviewed in 1942. It then already appeared to be a standard book of reference. This opinion is confirmed by the second edition,¹⁵ which has just appeared. Six new contributors and practically all of the old ones have written the text. The volume has increased by some 60 pages. As a matter of interest, the first introduction was written by Frederick Banting. The foreword to this second edition is by Charles H. Best. As heretofore, understanding, diagnosis and treatment of the various metabolic disorders are discussed. Two new chapters have been added, one on the thyroid and its diseases; the other, on disorders of the kidney.

During the five years which have elapsed, understanding of the role of proteins in wound healing, in the development of immunity, and in controlling the rate of convalescence, has greatly increased. Some advances in knowledge of nutrition and its deficiencies has taken place. In the present volume, the importance of folic acid has been noted. Alloxan diabetes is described. As heretofore, no attempt to include endocrinology as a whole has been made but wherever endocrine disturbances affect metabolism, this has been incorporated. The new edition has considerably increased the value of this important guide and certainly has brought it up to date.

R. T. FRANK.

Excerpta Medica¹⁶ is a new monthly review of the world literature dealing with radiology. This is Volume I, No. 1, Section 14 of this undertaking. The active editors

¹³*Die Hormonalen Aspekte des Fortpflanzungsprozesses*, von Dr. Jules Samuels, Chirurg-Frauenarzt, Spezialarzt für endogene Endokrinotherapie. 152 pages. Holdert & Co. N. V., Amsterdam, Holland. 1946.

¹⁴*Osteophthsis Pelvis et Femorum*. .Zugleich ein Beitrag zur Frage der Spontanen Rückbildung Maligner Tumoren. von Dr. Gottfried Hartmann, Assistent Des Pathol. Anat. Institutes der Universität Wien. Mit 19 Abbildungen. Wiener Beiträge zur Pathologie und Pathologischen Anatomie. Bd. 1. 183 pages. Wilhelm Maudrich, Wien, 1947. Distributors in U. S. A., Grune & Stratton, Inc., New York.

¹⁵*Diseases of Metabolism. Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner*. Edited by Garfield G. Duncan, M.D., Director of Medical Division, Pennsylvania Hospital; Clinical Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania. With Contributions by Walter Bauer, Hugh R. Butt, Abraham Cantarow, Tracy Donald Cuttle, Garfield George Duncan, Frank Alexander Evans, Ferdinand Fetter, Joseph Marchant Hayman, Jr., Martha A. Hunscher, Friedrich Klemperer, Cyril Norman Hugh Long, Perry MacNeal, Edward H. Mason, Max Miller, Louis H. Newburgh, John Punnell Peters, W. D. Robinson, Tom D. Spies, Leandro Maués Tocantins, Abraham White, Alexander W. Winkler. Second Edition, illustrated. 1045 pages. W. B. Saunders Co., Philadelphia. 1947.

¹⁶*Radiology being Section XIV of Excerpta Medica*. A complete monthly abstracting service of the world medical literature comprising fifteen sections and covering the whole field of theoretical and clinical medicine. Under the general editorship of M. W. Woerdeman, M.D., F.R.N.A.S., Professor of Anatomy and Embryology in the University of Amsterdam, Chairman. A. P. H. A. De Kleyn, M.D., F.R.N.A.S., Professor of Oto-, Rhino-, Laryngology in the University of Amsterdam, W. P. C. Zeeman, M.D., Professor of Ophthalmology in the University of Amsterdam. Vol. I, No. 1, Section XIV, June, 1947. N. V. Excerpta Medica, Amsterdam C. (The Netherlands).

objective, sober, and carefully worked-out fashion. Its format, many colored illustrations, and minute chapter bibliographies are rarely found in these days of paper shortage. The literature, particularly the American literature, has been utilized to a great degree, but in such a fashion as to not interfere with smooth reading.

The main subjects dealt with are embryology, anatomy, and physiology of the female; the separate endocrine glands; and finally, the female sex hormones. Childhood and adolescence, and maturity and senility are taken up in turn. The menstrual cycle is divided into uniphasic (anovular); biphasic (follicular and corpus luteum phase); and triphasic which constitutes pregnancy. In the description of glands, the treatment is equally thorough and consecutive. Under the chapter on thyroid, the authors have not as yet included thiouracil and its derivatives. The chemistry of the estrogens and progesterone is taken up in great detail. Among the endocrine glands, the authors justly place the chorion-placental system which is so often treated in a stepchild fashion. At the end there is a miscellaneous agglomeration of aphorisms which are both amusing and instructive. For example, they mention that the relation between the spermatozoan and the entire volume of man is 1:1,000,000,000.

This volume fills a definite gap in the Spanish literature. It should serve to keep the Spanish reading readers fully informed both of the newest knowledge in female sex endocrinology, as well as the world's literature, in a very pleasant, readable volume.

R. T. FRANK.

Cameron's *Recent Advances in Endocrinology*,¹¹ which is one of the Blackiston *Recent Advances Series*, has its sixth edition after an interval of only two years. This compact small volume is replete with information, and has gradually assumed a useful balance between investigative and laboratory versus clinical data so that today it has become a useful book for reference, particularly for those who are not able to keep up fully with the literature. In this connection it would be well if the index were made more detailed and if an index of authors were added.

The new edition coming so soon after the previous one shows comparatively little changes among the few new acquisitions. The production of artificial iodo-proteins and the employment of thiouracil should be mentioned. Each short chapter bibliography has been brought right up to date.

As I have previously mentioned, these *Recent Advances Series* occupy a position between the so-called yearbooks and more detailed treatises. They have a distinct advantage over the yearbooks in that continuity is kept up so that the full subject is dealt with. Cameron, who is professor of biochemistry, Medical Faculty of the University of Manitoba, is in intimate contact not only with the English but also with the American literature, which is of advantage to the reader.

R. T. FRANK.

A 540-page compendium on "The Endogenous Endocrinotherapy Including the Causal Cure of Cancer" from the pen of Jules Samuel of Amsterdam¹² has been published. To my mind this would show that the credulity of people in Europe is about on a par with that found in the Western Hemisphere. This large volume is a continuation of the publications of this author which have appeared since 1936. It is to precede the publication by this same author of five volumes giving the complete and extensive description. The entire method is based on a spectroscopic examination of the blood, which is supposed to show various deficiencies and ailments at a preclinical stage. This book is written in English.

R. T. FRANK.

¹¹*Recent Advances in Endocrinology*. By A. T. Cameron, C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Sixth Edition. 443 pages. With 74 figures, including Three Color Plates. The Blackiston Company, Philadelphia and Toronto. 1947.

¹²*Endogenous Endocrinotherapy including the Causal Cure of Cancer*. Compendium. By Dr. Jules Samuels, Specialist for endogeneous endocrinotherapy. Amsterdam. 540 pages. Holdert & Co., Amsterdam. 1947.

therapy including blood plasma, transfusion, and the various blood substitutes. Technical details are fully entered into. There is a copious bibliography. This monograph should be valuable to the Spanish-speaking readers.

R. T. FRANK.

Feminine Psychology²⁰ is an ecstatic and dramatized depiction of the art of attracting, conquering, and conserving love. Its appeal is not to a medical circle of readers.

R. T. FRANK.

²⁰Psicología Femenina. Arte de Atraer, Conquistar Y Conservar el Amor. By María J. Obregon de Marin. Imprenta La Milagrosa, Habana. 1944.

are all from Amsterdam, while the Board covers the entire globe. The object is to incorporate every article on radiology appearing in the medical literature of the world. Some will be included by title only, the more important to be in the form of informative abstracts, but condensed so as to be easily read. Each contribution will bear the signature of the specialist who has prepared it. The review is to go back to 1940 in order that the articles which appeared during the war and the articles that were frequently inaccessible may be included. Not only is general radiology, but radiological diagnosis of each of the body systems, and finally radiotherapeutics are included.

R. T. FRANK.

It seems a far cry from gynecology and obstetrics to *The Foot and Ankle, Their Injuries, Diseases, Deformities and Disabilities* by Lewin.¹⁷ However, if for no other reason, a short chapter on *The Relationship of Foot and Ankle Conditions to Urology, Gynecology, and Obstetrics* would warrant this review if any apologies were necessary. This thoroughly revised edition incorporates within its pages the vast knowledge gained through World War II. This includes the use of chemotherapy as a prophylactic and curative agent, the free use of plasma, etc. In the new edition there has been a revision particularly on compound fractures crushing wounds, osteomyelitis, and ringworm, both as a primary and secondary condition. The main object of the book is to act as a guide for medical officers of the armed forces. To show how the specialties have become aware of general medicine, there are interesting discussions of psychosomatic problems; neurological lesions; deficiency, metabolic and glandular diseases; dermatological affections and particularly changes of interest to the gynecologist and obstetrician. The relation of back, pelvis, hip, thigh, knee, to the foot and ankle.

R. T. FRANK.

Boyd's *Surgical Pathology*¹⁸ has a sixth edition after an interval of five years. This popular and standard textbook has always aimed to give the surgeon an insight into live pathology. It had this aim and hope long before the American Board emphasized this branch of medicine and insisted that the surgical specialist have this training.

In the present edition the pathology and pathologic physiology of the heart diseases has been given new chapters because of the rise of surgical interest in these conditions. Among the new material are included tumors of the larynx, pinealoma, Bittner's milk factor in relation to breast carcinoma, avitaminosis in cancer of the mouth, the Papanicolaou vaginal smear method in the diagnosis of carcinoma of the cervix, fibrous dysplasia of bone, inflammatory nodules of muscle in chronic arthritis, and fibrositis of the back. The book, as previously, is well written has 530 illustrations, and chapter bibliographies.

R. T. FRANK.

Massons has written a monograph which is an Introduction to the *Study of Intravenous Therapy*.¹⁹ It is a concise, well-written description covering every phase of intravenous

¹⁷*The Foot and Ankle. Their Injuries, Diseases, Deformities and Disabilities.* By Philip Lewin, M.D., F.A.C.S., Associate professor of Bone and Joint Surgery, and Acting Head of Department, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital; Attending Orthopaedic Surgeon, Cook County Hospital; Senior Attending Orthopaedic Surgeon, Michael Reese Hospital, Consulting Orthopaedic Surgeon, Municipal Contagious Disease Hospital, Chicago; Formerly Colonel, Medical Corps, Army of United States. With 389 illustrations. Line Drawings by Harold Laufman, M.D., F.A.C.S., Associate in Surgery, Northwestern University Medical School; formerly Major, Medical Corps, Army of the United States. Third Edition, thoroughly revised. 847 pages. Lea & Febiger, Philadelphia. 1947.

¹⁸*Surgical Pathology.* By William Boyd, M.D., Dipl. Psychiat., M.R.C.P. Edin., F.R.C.P. Lond., LL.D. Sask., M.D. Oslo, F.R.S.C. Professor of Pathology, The University of Toronto. 6th edition. With 530 illustrations including 22 color figures. 858 pages. W. B. Saunders Company, Philadelphia and London. 1947.

¹⁹*Introducción al Estudio de la Plasmoterapia.* par José M. Massons. De la Sección de Farmacología del Instituto de Investigaciones Médicas de la Universidad de Barcelona (Fundación de la Excm. Diputación). Prólogo de Francisco García-Valdecasa. Catedrático de Farmacología de la Facultad Médica de Barcelona. 276 pages. Miguel Servet, Barcelona. 1947.

the internal cervical os. The cervical canal was filled with fresh blood clots. The external os was soft, admitting the tip of the index finger. The diagnosis was central placenta previa with hemorrhage.

In an attempt to retrace the symptomatology and course of this unusual case, one may draw the following conclusion: this was apparently a case of central placenta previa at term with, at first, a concealed retroplacental hemorrhage. This was responsible for the severe abdominal pain, general distress, and rise in temperature. Later, external hemorrhage occurred throwing the patient into irreversible shock, followed by death.

In summary a case of central placenta previa with profuse hemorrhage, followed by death, is reported. Except for one rectal examination, the patient had no vaginal examination or any other manipulations. Autopsy showed the only pathology to be that of central placenta previa with evidence of hemorrhage. The congestion and edema of the lungs were probably secondary.

SIMON BRODY, M.D.

842 EASTERN PARKWAY
BROOKLYN, N. Y.
OCTOBER 6, 1947.

Nutritional Deficiency and Menstrual Disturbances

To the Editor:

In the October, 1946, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY (page 611) R. R. Greene and B. M. Peckham presented a "critical review" of our work on the relation of nutritional impairment of hepatic function to menorrhagia and other endocrine disturbances. By coincidence, the October issue of the *Journal of Dental Medicine* carried a quotation from William James which is so apt that I requote it here:

"There are three stages in the history of every medical discovery. When it is first announced, people say it is not true. Then, a little later, when its truth can no longer be denied, they say it is not important. After that, if its importance becomes sufficiently obvious, they say, 'Anyhow, it is not new.'"

The critique by Greene and Peckham, when viewed chronologically in relation to the three basic elements of this problem, is in remarkable accord with William James' analysis. Thus, that the healthy liver inactivates estrogen is now considered by them to be so well established, it is no longer new. That the livers of animals deficient in vitamin B complex cannot inactivate estrogen is also admitted to be true, but they say, the effect is due solely to the accompanying inanition, so it is unimportant. And, as for the etiologic relation of nutritional deficiency to menstrual disturbances, this is so fantastic, they say frankly, we don't believe it.

But Greene and Peckham were not content with permitting the subject to rest, so far as they are concerned, in the realm of opinion. They have contrived a scathing condemnation of our clinical observations and have attempted to bolster their derogatory views with a variety of superficially plausible objections. Unfortunately, their objections are of necessity purely theoretical, since nowhere in their "review" is there any indication that either the authors (or the equally caustic discussant) investigated even a single human case to determine whether there is any correlation between the lesions of nutritional deficiency and the endocrine disturbances, or to find out whether the latter responds to nutritional therapy.

Apparently Greene and Peckham knew of only one clinical study on the subject other than ours, that of Ayre and Bauld, and they are much incensed at the fact that these workers obtained results in agreement with ours; this paper too is dismissed as too fantastic for credibility. But other studies on the subject were available at the time their paper was presented, had they troubled to search the literature. For it seems that whenever the subject has actually been investigated and not simply dismissed, results similar to ours have been obtained (P. M. Sosa and M. B. Monserrat: *Prensa Med. Argentina* 31: 2657, 1944; H. Peters and W. Footers: *Permanent Found. Med. Bull.* 3: 137, 1945; M. Hellman: *Prensa Med. Argentina* 32: 1447, 1945).

Correspondence

Management of Placenta Previa

To the Editor:

In his report on "The conservative management of some varieties of placenta previa" (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 50: 248, 1945), H. W. Johnson states: "In conclusion may I, for statistical purposes, make the following request? Will you please report to me any fatal case of placenta previa which you may know about, where there had been no cervical nor intrauterine manipulation, nor any attempt at manual removal of remaining placental tissue during the third stage of labor. . . . This offer has been made many times during the last fifteen years, and at many of the 'refresher courses' offered by the State of Texas several years ago. These courses were attended by many of the older practitioners. I have, as yet, no case with which to start the series. Certainly, somewhere, sometime, someone must have died from placenta previa without having received energetic or heroic treatment."

A case meeting Dr. Johnson's "requirements" has come to my attention. I am reporting it, not so much with the view of having the distinction of starting Dr. Johnson's series, but rather because the case has general points of interest worth recording.

S. L., a 34-year-old white woman, was admitted to the Crown Heights Hospital, Brooklyn, on June 25, 1946, at 12:30 A.M. complaining of severe abdominal distress, worse on breathing. The patient was a gravida ii, para i. She had a child, 4 years old. Her last menstrual period was Sept. 20, 1945; the expected date of delivery was June 27, 1946. The prenatal course was uneventful except for an episode of slight vaginal bleeding about four weeks prior to admission. The patient was instructed at that time to rest in bed and report any further bleeding to her attending physician. On the night of admission, the patient felt well, ate a hearty meal, and was sitting outdoors with her neighbors. At midnight she began to feel abdominal pains and discomfort, which became rapidly worse. She was rushed to the hospital. Upon admission examination by the house resident revealed a short, stout woman, acutely ill, cyanotic, with labored breathing. Her temperature was 104.4; pulse 130; respirations 35. Heart sounds were normal. Lungs were clear; no râles were audible; no dullness on percussion. Abdominal examination revealed a full-term uterus which was hard and tender. Fetal heart was heard over the left lower quadrant, 140 per minute, of good quality. Rectal examination showed the cervix high and soft. The dilatation could not be definitely ascertained. Fifteen minutes after admission, while the patient was being shaved, she had a profuse hemorrhage from the vagina. The bedclothes were thoroughly soaked with blood. A few minutes later, the patient had an involuntary bowel movement.

The patient was seen by me about one-half hour after the bleeding episode. She was in complete shock, restless, tossing in bed, and gasping for breath. Her skin was cold and clammy. Her pulse was imperceptible at the wrist. Her blood pressure was unobtainable. The uterus felt hard and contracted. The fetal heart sounds were inaudible. There was no active vaginal bleeding at that time. The patient was given $\frac{1}{4}$ grain of morphine sulfate. Blood plasma was administered intravenously. Blood typing and RH factor determinations were ordered. The patient failed to respond to the medication and plasma injection, and expired about twenty minutes later.

An autopsy was performed and the positive findings were as follows: Congestion and edema of the lungs. The uterus contained a full-term male fetus in the left occipitoanterior position. The placenta was lying in the lower pole of the uterine cavity, completely covering

errors up to 1,000 per cent, especially as the quantities of estrogen available from blood and urine are so small as to forbid the use of a sufficient number of animals. Improved techniques may eventually make such methods more generally useful, but at present—analogueous to the clinical versus laboratory diagnosis of nutritional deficiency—the patient's own endometrium seems at least as reliable an indicator of her endocrine status, as the tissues of a test animal.

MORTON S. BISKIND, M.D.

BETH ISRAEL HOSPITAL
NEW YORK 3, N. Y.
Nov. 8, 1947.

Replies by Drs. Greene, Peckham, and Huffman

To the Editor:

In writing the critical review we endeavored to be as objective as possible. Judging from the tone of Dr. Biskind's letter we did not succeed. We are sorry.

Dr. Biskind seems to imply that we are newcomers to this field and had no right to be critical. One of us, however, has long been interested in the subject of the effect of the liver on the metabolism of steroid hormones and has been a joint author with Dr. M. W. Burill of several publications on the subject (*Proc. Soc. Exper. Biol. & Med.* 44: 273, 1940; *Endocrinology* 28: 874, 1941; *Endocrinology* 31: 73, 1942; *Endocrinology* 30: 142, 1942). These had to do with the effect of the liver on testicular and adrenal steroids. They were not specifically concerned with the subject of the review and were therefore not mentioned.

Dr. Biskind considers us remiss in not thoroughly searching the literature. He quotes three articles in which he states results similar to his were obtained. The article by Peters and Footer appeared in the *Permanente Foundation Medical Bulletin* and was a general discussion article entitled *Gynecology in Industry*. Three paragraphs were devoted to the successful treatment of menorrhagia with vitamin B complex. No data were presented. We admit that we were remiss in not citing this article. We doubt, however, that under similar circumstances we would be able to find a similar article in a similar obscure publication with such a general title.

No search of the literature would have been necessary to find the articles by Hellman and by Sosa and Monserrat. They were well publicized in the November, 1946, issue of the *Abbott Laboratories "What's New."* Copies of this publication were sent to us and to every physician in the United States. One dealt with the treatment of mastalgia and dysmenorrhea with vitamin B complex and the other, the treatment of dysmenorrhea. The review had to do with B complex, menorrhagia, and cancer. These articles were, therefore, deliberately not included. Further comment does not seem necessary except to note that dysmenorrhea was not included by the Biskinds in the gynecologic conditions improved by B complex therapy.

Dr. Biskind has drawn inferences from our review that were not intended nor implied (fourth paragraph). We did not and do not believe that a concise summary is reprehensible; nor is a "statement that one phase of the work is still in progress." We condemned no one for conducting studies in human beings on the basis of animal experiments. We do believe, however, that the transfer of results obtained in the experimental animal to the human must be done with caution and with full realization of the possibility of species variations. This latter point may be very pertinent. An example may be found on some work published by Hooker, Drill and Pfeiffer (*Proc. Soc. Exper. Biol. & Med.* 65: 192, 1947) subsequent to the presentation of our review but several months prior to Dr. Biskind's letter. In experiments similar to those performed in the rat by the Biskinds these workers have demonstrated that the liver of the monkey (*Macacus rhesus*) is not able to inactivate estrogens. In these animals (a species much closer to man than is the rodent) the addition of vitamin B complex did not enhance this nonexistent ability.

Analysis of the arguments of Greene and Peckham reveals some curious twists of logic and actual misstatements of fact. Quotations from our articles are so presented as to give the impression that, for instance, a concise summary, or a statement that one phase of the work is still in progress, is somehow reprehensible. We are condemned for conducting nutritional studies in human beings on the basis of animal experiments, yet the basis for this condemnation is the animal experiments of Drill and Pfeiffer. The latter have claimed that the failure of inactivation of estrogen in the liver which we have reported in vitamin B complex deficiency (and which has been confirmed by numerous other workers) is due solely to the associated inanition and not to the vitamin deficiency. The discrepancies between the results obtained by Drill and Pfeiffer and the conclusions drawn from them by these authors, have been considered in detail elsewhere (*Vitamins & Hormones* 4: 147, 1946) and need not be presented here. Greene and Peckham claim further that "Two of the early symptoms of vitamin B complex deficiency are anorexia and loss of weight," a statement that is simply in contravention of the facts. It is implied on this assumption that our patients could not have had nutritional deficiency, since the majority were of normal weight and many even of excess weight. The occurrence of lesions of vitamin B complex deficiency (e.g., atrophic glossitis, cheilosis, peripheral neuritis) in well-nourished persons is so well known as hardly to merit further discussion. The visible lesions in our patients have routinely been recorded by Kodachrome photography and many of the photographs of nutritional lesions, together with photomicrographs of the estrogenic endometriums of the same patients, have either been published or presented publicly; hence there need be little argument about the occurrence of either the nutritional or the endocrine lesions in our patients, or of their response to nutritional therapy.

The data demanded of us as the price of winning the credence of authors and dissesant are truly fabulous. Intensive activity of the personnel of a well-staffed research institute could hardly supply all of it in the six and one-half years we have been working on the problem. Do the authors suggest withholding publication of our data simply because all its implications have not been investigated?

Further detailed discussion, point by point, of the questions raised by Greene and Peckham, would require an article at least as long as theirs, and almost all the issues raised by them have already been discussed at length elsewhere (*Vitamins & Hormones* 4: 147-185, 1946; *Am. J. Clin. Path.* 16: 737, 1946). But a few misconceptions, especially evident in the discussion, merit correction. First is the suggestion that the diets of our patients should have been analyzed or that vitamin excretion studies should have been done, conclusively to demonstrate nutritional deficiency. It is of course very well known that dietary deficiency per se (which was certainly common enough in our patients) is only one of a vast number of causes of nutritional deficiency.

Numerous studies have indicated that lesions of nutritional deficiency may be produced even in the presence of an adequate diet by factors which impair absorption of essential nutrients (e.g., gastrointestinal disturbances, biliary disease), or increase the requirement (e.g., pregnancy and lactation, hyperthyroidism, excessive physical activity, infections), or interfere with utilization (e.g., radiation therapy), or increase destruction (e.g., estrogens, sulfonamide drugs, industrial poisons) or excretion (e.g., lactation, excessive perspiration, polyuria). This subject has been reviewed by Norman Jolliffe (*Handbook of Nutrition*, Am. Med. Assoc., 1943, Chapter 24) and is summarized in a table in an article by Jolliffe and Most (*Vitamins and Hormones* 1: 80, 1943). As for vitamin excretion studies, it is equally well known that these are of limited value as the tests reflect tissue levels very erratically. When patients have lesions of vitamin deficiency that can be detected with the naked eye (e.g., cheilosis, glossitis, gingivitis, skin lesions) or with a vibrometer (early peripheral neuritis) why surrender clinical acumen to dubious laboratory data?

Second is the suggestion that estrogen assays should have been performed on our patients. There is no question that such studies meticulously performed, have been of great value. But they are extremely laborious and time-consuming and often yield data of doubtful validity, owing to cumulative chemical losses and biologic variability. The latter frequently involves

wide variety of gynecologic complaints and that it is of specific therapeutic value in these disorders. It is essential that any measures advocated for the prevention and/or treatment of a group of diseases including carcinoma of the uterus and functional metrorrhagia be examined with thoroughness. This is particularly true when the advertising literature of major pharmaceutical manufacturers carries the therapeutic advances to the general medical public. Such criticism is not made with the thought of deriding the advocates. A scientific theory worthy of perpetuation and acceptance certainly should be able to withstand any criticism directed against it. If it cannot then it is not a valid theory.

I have had occasion to observe a considerable group of women suffering from functional uterine bleeding. These studies were not concerned with the patient's nutritional state. However, it was my impression that these patients did not present clinical evidences of gross vitamin deficiencies; a review of their case histories confirms that opinion. That patients with gross nutritional deficiencies may have genital disorders is not questioned. However, I do not believe that most patients with gynecologic complaints can be shown to have clinical evidence of vitamin depletion. If a subclinical deficiency is to be demonstrated it would appear that analysis of the diet to show a vitamin lack and excretion studies would be the logical way to do it.

Drs. Greene and Peckham have commented on the photomicrographs of endometrial hyperplasia which Dr. Biskind has used as evidence of hyperestrinism. I agree with their comments. It is true that errors do occur in estrogen determination; it is also true that there may at times be some debate as to what constitutes endometrial hyperplasia. Also, many well-qualified gynecologists will question whether endometrial hyperplasia is always *prima facie* evidence of hyperestrinism.

I cannot accept Dr. Biskind's objection to the use of estrogen assays on the basis that they are extremely laborious and time consuming. Such difficulties, while perhaps slowing scientific efforts, should not stop them. It would surely not be too difficult to study a moderate-sized group of patients so that all critics would be satisfied.

I wish to reaffirm a statement previously made that I would welcome convincing evidence that a deficiency of Vitamin B complex is the cause and that its administration will cure these many gynecologic disorders.

J. W. HUFFMAN, M.D.

CHICAGO, ILL.

Dec. 5, 1947.

Leunbach's Paste

To the Editor:

In response to questionnaires to a large number of obstetricians and gynecologists concerning Leunbach's paste and similar preparations, the response was almost unbelievable in numbers and unanimity of opinion.

As a result of the information obtained from the questionnaires the Food and Drug Administration was able to embark on a campaign to rid the market of these murderous preparations. Our campaign was completely successful and resulted in removal of all such preparations from the market.

The originator of the business in this country, Adolph G. Schickert, was sentenced to a term in a Federal prison, and at the termination of his sentence was deported to Germany. Two other manufacturers served prison sentences, and the remaining two received heavy fines.

It would not have been possible to carry out this program without the wholehearted help and cooperation of a large number of obstetricians and gynecologists. Many of these very busy and public-spirited men left their practices to appear as witnesses for the Government in one or more of the trials which resulted from our regulatory efforts. Many other practicing obstetricians and gynecologists who were not called upon to testify for the Government gave their valuable time to answer our questionnaire and in advice and counsel. We would like to express our very deep appreciation to all of these physicians and to let them know that their efforts were not unavailing. It is not possible to communicate with each

Space limitations prohibit further pursuit of this particular subject but we cannot resist pointing out several facts or theories ignored by the Biskinds in formulating the hypothetical rationale for their clinical use of vitamin B complex. The first is the known ability of the kidney to excrete estrogens in the free as well as the combined form. They ignore the possibility that the kidney could excrete this "noninactivated" estrogen theoretically present in vitamin B complex deficiency. Secondly they ignore the commonly accepted ideas as to the reciprocal relationships between gonad and hypophyseal function. If an excess of estrogen did accumulate with vitamin B deficiency, in theory at least, it would depress the gonadotropic function of the hypophysis. The resulting depression of estrogen production should cause the estrogen level to return to normal and the same mechanism should maintain it at a normal level. This latter subject is admittedly theoretical in nature. However, one would logically expect the Biskinds to explain its nonvalidity rather than to consistently ignore it.

According to Dr. Biskind our statement that two of the early symptoms of vitamin B complex deficiency are anorexia and loss of weight, is "simply in contravention of the facts." We freely admit that this statement as written was partially erroneous. We wish to apologize for our carelessness. Only one article of three references on which this statement was based referred to vitamin B complex (Speis, T. D., Vilter, R. W., and Ashe, W. F.: J. A. M. A. 113: 1931, 1939). The other two (Speis, T. D., Hightower, D. P., and Hubbard, L. H.: J. A. M. A. 115: 292, 1940; and Foltz, E. E., Barboraka, C. J., and Ivy, A. C.: Gastro-enterol. 2: 323, 1944) referred specifically to thiamin chloride deficiency. In the last article only anorexia was noted since the subjects were on a fixed caloric intake.

Dr. Biskind states that "many of the photographs of nutritional lesions, together with photomicrographs of the estrogenic endometriums of the same patients, have either been published or presented publically." We have not been privileged to hear one of Dr. Biskind's public presentations. At the time the review was presented (Dec. 20, 1946) no photomicrographs had been published. Subsequently we have been able to find three photomicrographs published in *Vitamins and Hormones* (4: 147, 1946). (This book was received by the Chicago Medical Book Company on December 22, 1946, and was available in the Northwestern University Medical School Library on January 7, 1947.) These photomicrographs are labelled either "cystic hyperplasia" or "glandular cystic hyperplasia." As evidence of excessive and/or prolonged estrogen stimulation, the last two of the three are not convincing. As well as can be judged by the magnification used the second shows sub-nuclear vacuolization. This finding in the human being is accepted as evidence of early progesterone stimulation. The third photomicrograph is representative of the late proliferative stage and shows the edema of the stroma characteristic of this phase and not the crowded, closely packed stromal nuclei of hyperplasia.

The remainder of Dr. Biskind's letter in reality refers to Dr. Huffman's discussion and not to the review, and will be discussed by him.

We regret that Dr. Biskind has chosen to be so vigorously affronted by our review. Merely in the interest of accuracy may we remind him that his December, 1946, article was not published in the *Archives of Pathology* as stated in his letter but in the *American Journal of Clinical Pathology*?

R. R. GREENE, M.D.

B. M. PECKHAM, M.D.

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL.
CHICAGO, DEC. 5, 1947.

To the Editor:

Dr. Biskind's criticism of my discussion of the paper by Drs. Greene and Peckham has been read with great interest. I sincerely regret that Dr. Biskind has apparently taken personal affront at what were intended for objective comments. The primary object of the discussion was to point out what appeared, from a clinician's viewpoint, to be loopholes in the scientific proof of the hypothesis that vitamin B complex deficiency is capable of causing a

wide variety of gynecologic complaints and that it is of specific therapeutic value in these disorders. It is essential that any measures advocated for the prevention and/or treatment of a group of diseases including carcinoma of the uterus and functional metromenorrhagia be examined with thoroughness. This is particularly true when the advertising literature of major pharmaceutical manufacturers carries these therapeutic advances to the general medical public. Such criticism is not made with the thought of deriding the advocates. A scientific theory worthy of perpetuation and acceptance certainly should be able to withstand any criticism directed against it. If it cannot then it is not a valid theory.

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one individually, so I am taking this opportunity to ask you if it would be possible to insert a notice in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* to inform these physicians who assisted us that the campaign was completely successful and to express our appreciation for their efforts.

We are fully aware that the highly lucrative returns from this type of business will tempt others to embark in this field. We have estimated that a tube of the preparation selling in the neighborhood of five dollars costs but a few cents to prepare for sale. We are, therefore, very much on the alert for the certain resurgence of this "racket," and you may be assured that when it appears the full resources of this Administration will be thrown into the battle to stamp it out.

G. A. GRANGER, M.D.
MEDICAL OFFICER.

FOOD AND DRUG ADMINISTRATION
WASHINGTON, D. C.
NOVEMBER 20, 1947.

Aspiration Curettage

To the Editor:

In the November, 1947, issue of the *JOURNAL*, Williams and Stewart, writing on aspiration curettage of the endometrium in a cancer clinic, refer to a report on office curettage by the undersigned. Williams and Stewart state: "They (Israel and Mazer) subject their patients to surgical dilatation and curettement without hospitalization. . . ."

May we take exception to the term, "surgical dilatation," which, to us, suggests a forceful act. The technique of office curettage described in the mentioned article does not include surgical dilatation. We state (*AM. J. OBST. & GYNEC.* 36: 445, September, 1938): "In multiparous women, the smallest (No. 1) Sims' sharp curette may then be passed without difficulty. However, in some nulliparous women, the cervical canal is narrow and requires preliminary dilatation. In such instances, the smallest metal dilator, moistened by a sterile water-soluble lubricant, is passed beyond the internal os. Following this, the curette readily enters the uterine cavity. . . ."

We do not regard surgical dilatation of the cervix as a feasible office procedure.

S. LEON ISRAEL, M.D.
CHARLES MAZER, M.D.

2116 SPRUCE STREET
TWENTY-FIRST AND SPRUCE STREETS
PHILADELPHIA, PA.
DECEMBER 1, 1947.

Estrogens in Dysmenorrhea

To the Editor:

In the article of Doctors Torpin, Woodbury, and Child on "The Nature of Dysmenorrhea" (*AM. J. OBST. & GYNEC.*, November, 1947), the authors erroneously credit Sturgis and Albright¹ with the discovery that "large doses of estrogens administered early in the cycle abolished ovulation, and that the subsequent period was quite painless." The original report of Sturgis and Albright, however, refers to an earlier article by Dr. Raphael Kurzrok and myself,² acknowledges our prior use of estrogens in dysmenorrhea and confirms our observations regarding ovulation and corpus luteum function.

I first began to use estrogens in the treatment of dysmenorrhea in 1934. The prevailing theory at the time attributed the condition to excessive estrogen action resulting from absence or hypofunction of the corpus luteum. Quite by accident one of my patients was given estradiol benzoate, as a result of which she experienced the first painless period of her life. Further trials convinced me that this type of therapy was not without merit and I began an investigation into its *modus operandi*.

described more or less independent muscles, attributing their names to different fibers, which was the practice in their times, e.g., Wilson, Guthrie, and Muller who described special perinurethral fibers.

No less an authority than Luschka described the transverse perinei as a part of the levator ani muscle while others considered it a completely independent muscle. However, Gegenbaur, in his textbook, laid it down "that a morphological unity of all the muscles of the perineum exists, inasmuch as they develop from the primitive sphincter cloacae muscle." This was the guiding principle which stimulated Popowsky in his research.

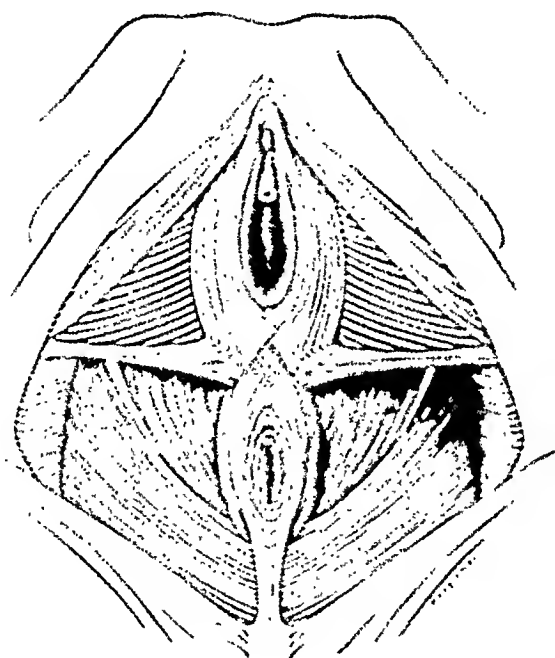


Fig. 1.—Schematic representation of the sphincteric muscular group of the pelvic floor. (Power, *Surge., Gynec. & Obst.*, Sept., 1916.)

Popowsky, working with a series of young embryos, term babies, and adults, was able to demonstrate the origin of the sphincteric vulval group as arising from a single subcutaneous muscle, the sphincter cloacae (Fig. 2). I have repeated a large part of this work in the anatomic laboratory of McGill University, and my results, as far as they go, confirm Popowsky's conclusions.

In the early embryo the allantois and the hindgut terminate caudally in a common cavity, the cloaca. This structure, of course, corresponds to that found in the adult reptiles and birds, in which the orifice is surrounded by a sphincteric muscle. In the human embryo the allantois becomes separated from the cloaca by the ingrowth of a transverse mesodermal bar, thus forming the rectum behind and the urogenital sinus in front. The sphincteric muscle as a distinct entity can first be seen in a two-month human embryo. For the most part, this primitive muscle completely surrounds the orifices of the urogenital sinus and anus, but already a few fibers can be seen to decussate between these

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of the Society of Obstetricians and Gynecologists of Canada, Ste.
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EMBRYOLOGICAL DEVELOPMENT OF THE LEVATOR ANI MUSCLE*

R. M. H. POWER, M.D., M.S., F.A.C.S., MONTREAL, QUEBEC

BY WAY of preamble, it is relevant to dwell briefly on the anatomic arrangement and functional development of the vulval sphincteric musculature (Fig. 1). This muscular group derives its origin from the common cloacal sphincter to which the levator ani muscle is inextricably related. Both the cloacal sphincter and the levator ani are ultimately derived from the third and fourth sacral myotomes.

The morphological work of Eggeling (1896) and the embryological investigations of Popowsky (1899) have elucidated the relationships of the vulval sphincteric group. From the "primordial sphincter cloacae" there arises, both in the course of phylogeny and of embryology, a division into a sphincter ani externus and a urogenital sphincter. The sphincter ani may differentiate into several layers and become a trilaminar muscle. The urogenital sphincter also differentiates further, but in a more decisive manner. From it are developed the sphincter urethrae, the ischiocavernosus of either side, and a median bulbo-cavernosus retaining a tendineus raphe in the midline, and probably the transverse perinei, superficial and deep.

Difference of opinion exists regarding not only these latter muscles themselves but also the question as to where they belong, their isolation, and non-isolation. Among others, Henle and Gegenbaur recognized the existence of a single muscle placed around the membranous part of the urethra, while others

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

transverse perinei muscle is formed. The deep transverse perinei is the last of the perineal muscles to appear in the human embryo and most of its development occurs postnatally. These two muscles apparently represent a development from the sphincter vaginae.

Practically nothing is known of the origin of the urogenital diaphragm. In some of the lower apes the fascia on the caudal aspect of the pubocaudalis muscle forms a diaphragm in this region, but it is very doubtful if this is homologous with the human urogenital diaphragm. Wesson showed that in early life the human urogenital diaphragm is poorly developed and later acquires its characteristic density and strength. He regards it as a functional development, arising in man consequent to the upright posture and formed by a condensation of the fascia surrounding the muscles. The muscle mass in the embryo is covered on both aspects by a primitive connective tissue and in response to the functional requirements of the area, these sheets of connective tissue probably differentiate into the strong fascial lines of the urogenital diaphragm.

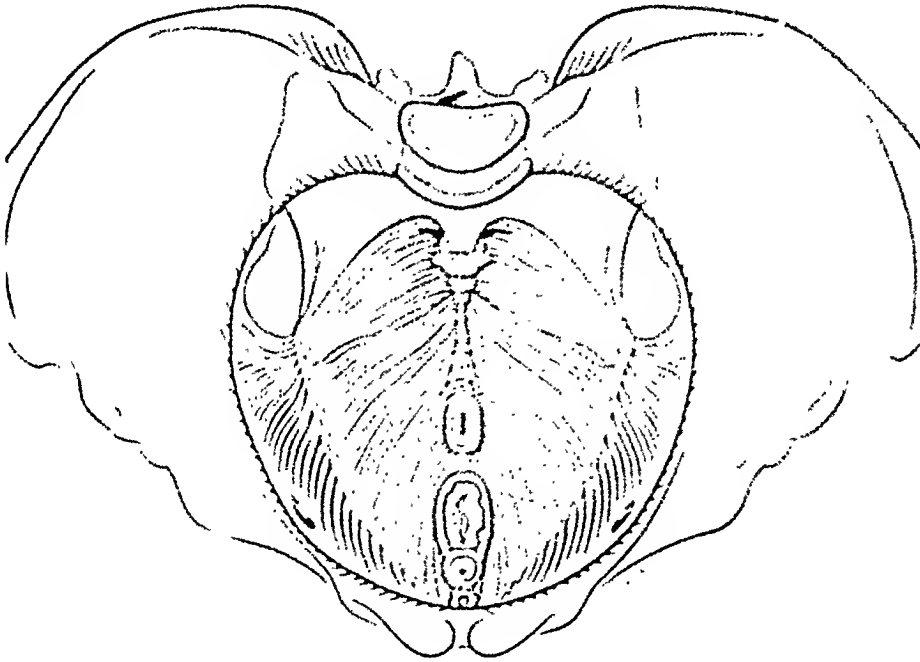


Fig. 3.—Levator ani muscle seen from above. Note anteriorly how pubococcygeal fibers are attached directly to the os pubis. Pubovaginalis and puborectalis fibers are clearly defined.

Davies describes the urogenital diaphragm as a continuity of the endopelvic fascia. This throws no light on its origin and is merely a statement that the various fascial layers in the pelvis are continuous with each other. This is a very usual phenomenon throughout the whole body.

In the lower monkeys the tail musculature is well developed and helps to support the viscera. It is composed of a strong pubocaudalis extending from the pubis to the tail and more laterally placed abductor caudalis muscles. The pubocaudalis passes beside the rectum but has no or only very slight attachments to it. In the anthropoids an anococcygeal raphe is present. The well-defined pubocaudalis finds some attachment to the rectum. The iliococcygeus and

two openings. The primitive cloacal sphincter is thus beginning to divide into a sphincter ani externus behind and a sphincter of the urogenital sinus in front.

With the sphincter ani externus we have no further concern. As already stated, it differentiates into a trilaminar muscle. Coming to the sphincter of the urogenital sinus, we may note that shortly after the sinus opens on the surface of the embryo, the ventral end of this muscle gains a slight attachment to the precartilaginous anlage of the os pubis. The ventral-caudal end of the urogenital sinus becomes differentiated into the urethra. Consequently, the ventral part of the urogenital sphincter develops into the sphincter of the urethra and migrates to a deeper plane. At a somewhat later date the conjoint caudal end of the Müllerian ducts which have made contact with the dorsal surface of the urogenital sinus push their way down along the posterior wall of the sinus to form the vagina; the dorsal end of the sphincter of the urogenital sinus surrounds the opening of the primitive vagina and differentiates into the sphincter vaginae or bulbocavernosus muscle. The sphincter of the urethra and the sphincter vaginae are still structurally continuous and are attached ventrally to the primitive pubis and from these the ischiocavernosus muscle develops.

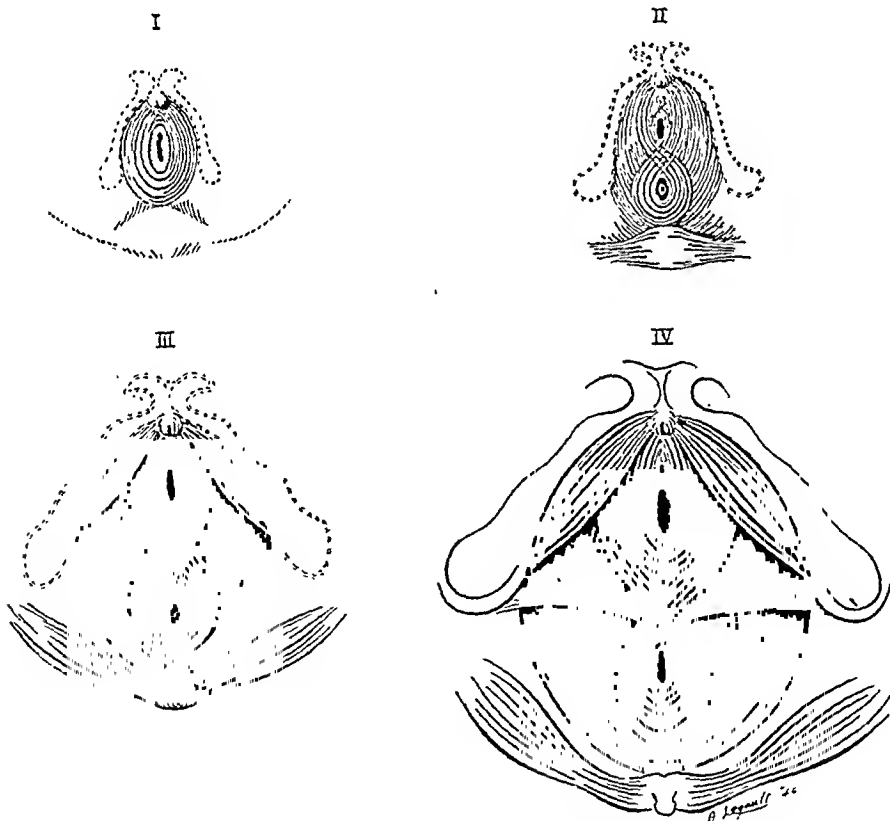


Fig. 2.—Successive differentiation of the cloacal sphincter in embryos of two, three, five, and seven months.

In the anthropoid apes the sphincter ani extends forward and forms a muscular diaphragm closing in the subpubic angle, and no true transverse perinei muscles are formed. In man this forward extension of the sphincter ani is not found, and instead we find that first a superficial and then a deep

segments is both phylogenetically and ontogenetically the oldest in the body. The development of many of the muscles in man and animals has never been traced and of the remainder our knowledge is fragmentary and incomplete.

The levator ani muscle is an evolutionary product representing the caudal flexor, abductor musculature of tailed mammals, which in man, as in anthropoid apes, with the reduction of the tail, has gained new relationships with the pelvic viscera. The coccygens represents the proximal ventral caudal abductor of tailed mammals. No effort to verify the former statement in the human fetus is recorded in the literature to my knowledge.



Fig. 5.—Gorilla's pelvis seen from behind.

Let us for a moment consider the recti group of the thoracoabdominal muscles which arise through the ventral extension of the thoracic myotomes into the body wall.

Certain fundamental processes are operative in the changes of the myotomes during the formation of adult muscles. Such processes may consist of a change in the direction or a migration of myotomes, fusion of portions of successive myotomes as in the formation of the rectus abdominis muscles, or a longitudinal or tangential splitting, or a degeneration of myotomes.

coccygeus show tendinous changes. In man the pubocaudalis attains its maximum attachment to the rectum and forms a true puborectalis, while the ilio-coccygeus and coccygeus show further muscular and fascial regression. In its morphologic development the pubocaudalis experiences a regression in muscular elements with a compensatory development of tendon and fascia (Fig. 3).



Fig. 4.—Lateral view of (A) great anthropoid, and (B) human pelvis. Note high cup-shaped arrangement of levator ani muscle in anthropoids with large external sphincter and cephalad termination of sacrum. In the human being the external sphincter is smaller and the triangular ligament is present, the sacrum is wider and terminates more caudally. Notice rotation of ilium in the human being.

To summarize, in the anthropoids the sacrum is situated very cephalad to the ischium; the pelvic outlet accordingly is a very elongated lozenge, the dorsal end being much cephalad to the ventral, and is weak, especially posteriorly. This is compensated for by an exceptional development of the sphincter ani externus which extends forwards as a muscular diaphragm into the urogenital area (Fig. 4). In man the bony pelvis is greatly shortened in a cephalic caudal direction and the wider sacrum terminates at a relatively lower level. The outlet, therefore, is very much shortened dorsoventrally, but is relatively broadened from side to side, especially in the anterior part. The pubocaudalis now is mainly attached to the rectum and anococcygeal body; the iliococcygeus has also moved its insertion on to the side wall of the anal canal and anococcygeal body, and the coccygeus muscle itself is more tendinous and forms the lesser sacrosclatic ligament. Compare, for example, a gorilla with a human pelvis (Fig. 5). Notice in the gorilla how cephalad the sacrum terminates; the complete absence of an ischial spine; the absence of a true sciatic notch, and the elongation of the whole pelvis as compared to the human being. In man the sphincter ani externus is much reduced and does not form a diaphragm, and in its place we find the deep and superficial transverse perinei muscles, and the urogenital diaphragm.

The skeletal musculature is derived almost entirely from the primitive segments. These may be said to begin with the segmentation of the dorsal divisions of the trunk mesoderm. The musculature arising from the primitive

The myotomes begin to grow into the body wall with the development and extension of the ribs. Even in a 7-mm. embryo, before the myotomes are fused into a continuous column, this process has already begun. In a 9-mm. embryo the myotome process extends further ventrally than do the ribs and ends ventrally in a continuous column on each side--the "rectus element" formed by the fusion of the entire myotome thickness.

This ventral longitudinal muscle column of each side ultimately forms the rectus abdominis and pyramidalis in the abdomen, the depressor muscles of the hyoid bone in the neck, while in thorax, owing to the development of the sternum, is not represented or is represented very occasionally by a vestigial sternalis muscle. At this early stage of the embryo we may note that the cloacal membrane is still on the caudal edge of the umbilical cord (Fig. 7). The primitive longitudinal ventral muscle column, therefore, extends between the two openings of the primitive alimentary canal; from the mouth to the primitive cloacal membrane. At a later stage the cloacal membrane migrates caudally into the perineum, and as it does it carries with it the original ventral cleft between the muscle column of either side. Thus are formed the lower part of the linea alba with the rectus abdominis muscles on either side.



Fig. 8.—X-ray photograph. Note absence of pubic element on right side.

The levator ani muscle, as shown by its nerve supply, is undoubtedly derived from the fourth sacral myotome, and it is tempting to suggest that as this myotome migrates ventrally it becomes divided like the myotomes of the abdominal wall, into two portions: a lateral part, the iliococcygeus, forming a continuous sheath and corresponding roughly to the oblique muscles of the abdominal wall; and a ventral longitudinal column, the pubococcygeus, or pubo-caudalis of lower forms, corresponding approximately to the rectus abdominis. If this view is substantially correct, the anovaginal cleft between the pubo-coccygeus of either side really corresponds to an extension of the linea alba, which was later cut off from the abdominal linea alba by the development of the

As the body wall develops, extensions of the myotomes migrate ventrally into these walls and the ventral ends of these extensions fuse together to form a ventral longitudinal muscle column from which the rectus abdominis and other elements are ultimately developed (Fig. 6).

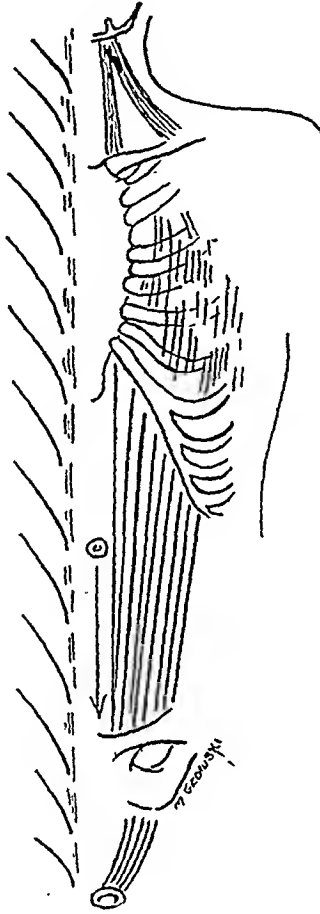


Fig. 6.—Right side undifferentiated ventral longitudinal muscle column. Left side differentiated ventral longitudinal muscle column.

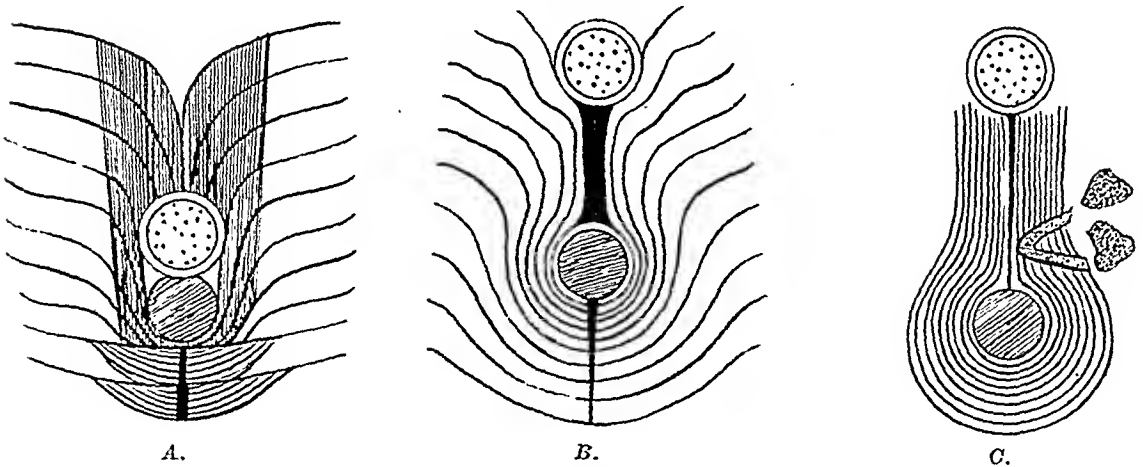


Fig. 7.—Diagrammatic representation of the formation of the lower end of the linea alba and the anovaginal cleft. A. The cloacal membrane extends onto the caudal surface of the umbilical cord. B. The cloacal membrane has migrated ventrally forming the upper end of the linea alba below the umbilicus. C. The cloacal membrane has reached the perineum. The pubic element growing in from the side cuts off the lower end of the linea alba to form the anovaginal cleft. (Dotted center represents the umbilical cord. Cross-hatched circle represents the cloacal membrane.)

The myotomes begin to grow into the body wall with the development and extension of the ribs. Even in a 7-mm. embryo, before the myotomes are fused into a continuous column, this process has already begun. In a 9-mm. embryo the myotome process extends further ventrally than do the ribs and ends ventrally in a continuous column on each side—the “rectus element” formed by the fusion of the entire myotome thickness.

This ventral longitudinal muscle column of each side ultimately forms the rectus abdominis and pyramidalis in the abdomen; the depressor muscles of the hyoid bone in the neck, while in thorax, owing to the development of the sternum, is not represented or is represented very occasionally by a vestigial sternalis muscle. At this early stage of the embryo we may note that the cloacal membrane is still on the caudal edge of the umbilical cord (Fig. 7). The primitive longitudinal ventral muscle column, therefore, extends between the two openings of the primitive alimentary canal; from the mouth to the primitive cloacal membrane. At a later stage the cloacal membrane migrates caudally into the perineum, and as it does it carries with it the original ventral cleft between the muscle column of either side. Thus are formed the lower part of the linea alba with the rectus abdominis muscles on either side.



Fig. 5.—X-ray photograph. Note absence of pubic element on right side.

The levator ani muscle, as shown by its nerve supply, is undoubtedly derived from the fourth sacral myotome, and it is tempting to suggest that as this myotome migrates ventrally it becomes divided like the myotomes of the abdominal wall, into two portions; a lateral part, the iliococcygeus, forming a continuous sheath and corresponding roughly to the oblique muscles of the abdominal wall; and a ventral longitudinal column, the pubococcygeus, or pubocaudalis of lower forms, corresponding approximately to the rectus abdominis. If this view is substantially correct, the anovaginal cleft between the pubococcygeus of either side really corresponds to an extension of the linea alba, which was later cut off from the abdominal linea alba by the development of the

os pubis. The longitudinal muscle column of either side, therefore, still extends morphologically between the two openings of the alimentary tract, but is interrupted at two places—one, by the formation of the sternum, and two, by the formation of the os pubis. In other words, as the cloacal membrane migrates from the umbilical cord to the perineum it carries with it, so to speak, an extension of the linea alba, and also an extension of the tendency of the myotomes



Fig. 9.—Dissection of eviscerated fetus. Diagrams A, B, and C with fetus tilted at varying degrees show continuity of rectus abdominis fibers terminating in right puborectalis muscle. *a*, Rectus abdominis fibers. *b*, Puborectalis fibers.

In support of this view we may note that in the selacians, the pelvic floor is formed by a backward continuation of the rectus abdominis. (Kieth and Paramore, *Lancet*, May, 1910.) The pelvic part of the rectus is attached behind to the tail; anteriorly it is attached to the movable pelvic girdle. The cloaca of the dogfish passes out between the right and the left primitive representatives of the levator ani, which can compress the cloaca, not by depressing the tail, as in mammals, but by pulling the pelvis backwards. This would make the pubocaudalis simply a caudal continuation of the rectus abdominis element.

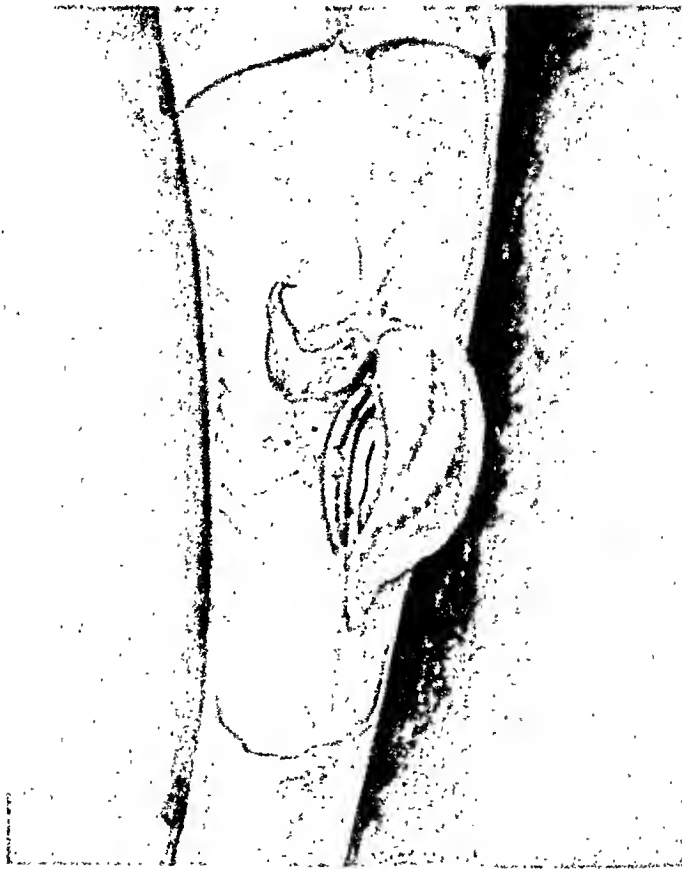


Fig. 13.—Drawing of adult dogfish, ventral surface. M.: Myotome. T.: Transverse pelvic bar. C.P.: Caudopelvic strand.

A pelvic floor can scarcely be said to exist in the fish, for the pelvis is rudimentary. In the dogfish (Fig. 13) the pelvic girdle is represented merely by a transverse bar of cartilage placed in front of the cloaca. It is unconnected with the vertebral column except by means of that part of the lateral trunk musculature which extends forwards from the tail into the body and which, as it passes over the pelvic bar, sends a good strand of its lowermost fibers to be inserted into its upper and lateral part. This strand of fibers, which forms part of the central tail musculature, from which it cannot be differentiated, is directed from behind forwards to the pelvic bar and may be called the caudopelvic strand.

Efforts have been made to follow the development of these muscles in detail in the human embryo and are still under way. We are not yet in a position to make a positive statement as regards the human embryo, but we have many indications that lend support to our view (Figs. 10, 11, and 12).

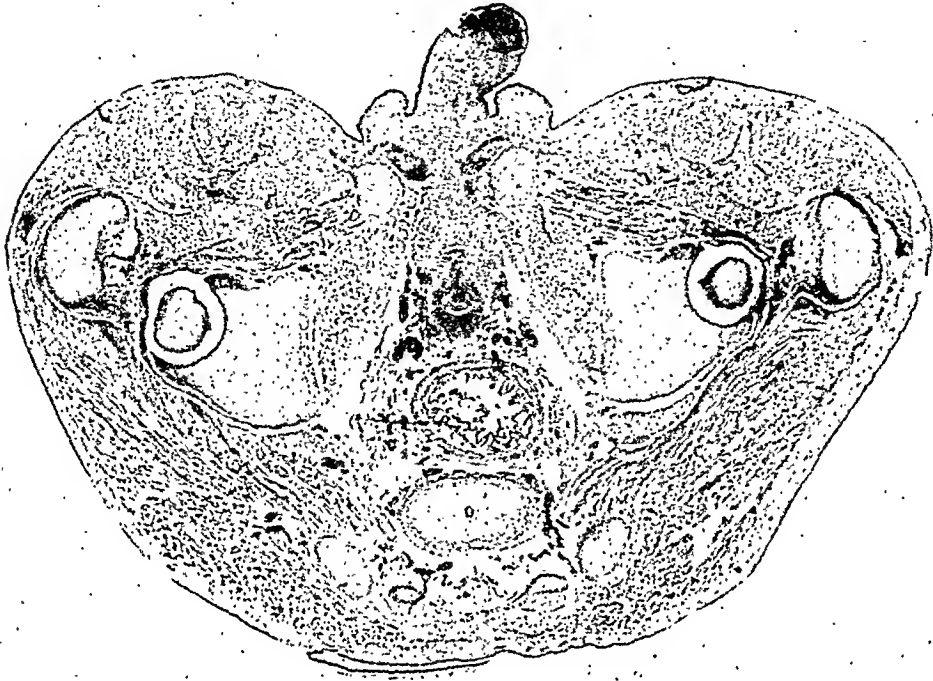


Fig. 11.—Two-and-one-half month fetus. Transverse section through acetabular region. Notice obturator internus muscle medial to which are the pubococcygeal fibers, extending antero-posteriorly.



Fig. 12.—Actual dissection of four-month fetus showing pubococcygeal and puborectalis fibers. In a younger fetus the caudal end of the vertebral column is almost vertically beneath the pubic element. Thus the puborectalis and rectus abdominis fibers are almost in a straight line.

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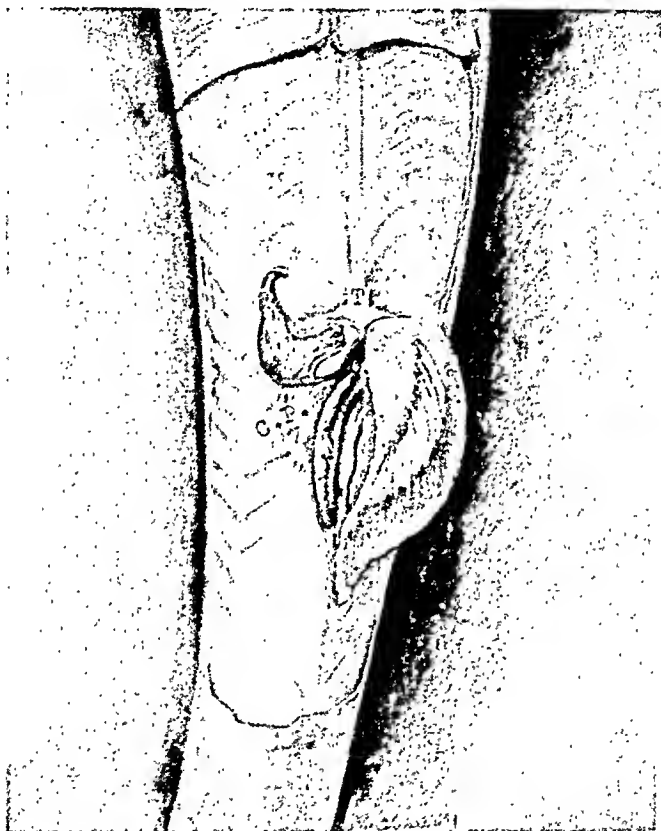


Fig. 13.—Drawing of adult dogfish, ventral surface. M = Myotomes. T = Transverse pelvic bar. C.P. = Caudopelvic strand.

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In amphibians the recti and puborectalis are in the same straight line, interrupted by the os pubis (Figs. 14, 15, and 16). The recti abdominis and external obliques are attached to the pelvis; their contractions can become efficient only by fixation of this structure. This fixation was primarily attained by the development of the caudopelvic muscles, which thus anchored the pelvis posteriorly. The caudopelvic muscles are relatively of considerable strength, and pass caudally from the pelvis almost in the same straight line as the recti abdominis, and thus are admirably adapted to resist a displacement of the pelvis forwards which contraction of the recti tends to bring about.

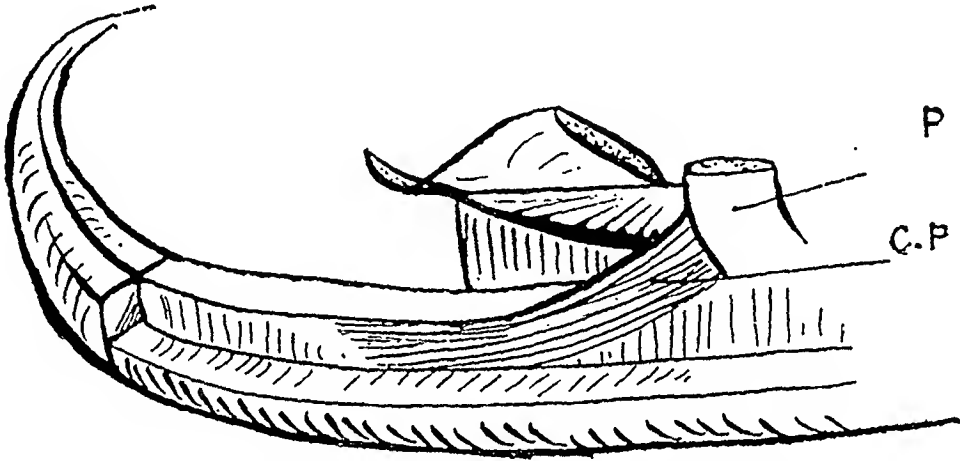


Fig. 14.—Dissection of cloacal region of the dogfish. About one-half life size. P = Pelvic bar bisected and turned outward. C.P. = Caudopelvic strand.

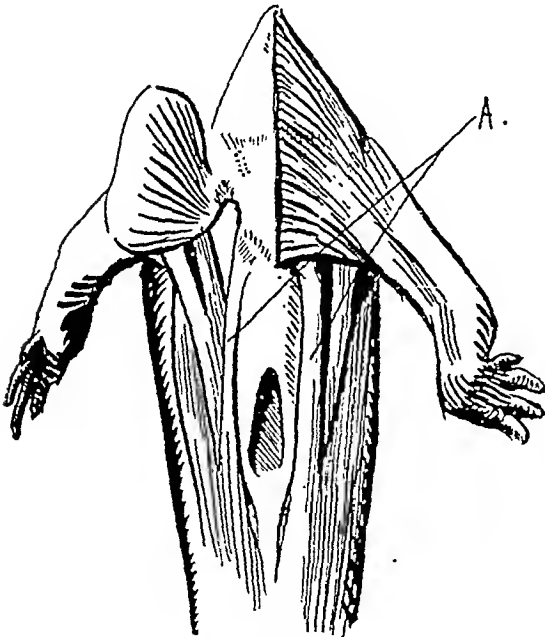


Fig. 15.

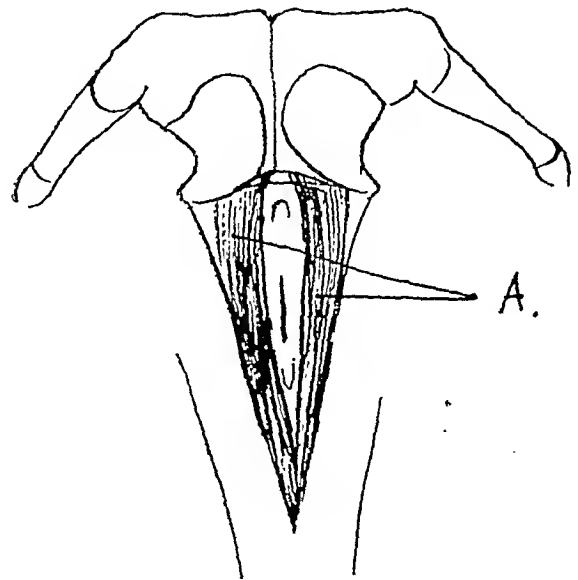


Fig. 16.

Fig. 15.—Dissection of menobranchius showing caudopelvic muscles. A, The cloacal passage has been cut through on a plane with these muscles, and the superficial parts have been removed.

Fig. 16.—Dissection of salamander maculosus to show A, caudopelvic muscles. (After Paramore.)

PLASMA PROTEINS IN PREGNANCY^{*}

J. L. MACARTHUR, M.D., MONTREAL, QUEBEC

PROTEIN metabolism has been under investigation for nearly one hundred years, but it is only recently that hypoproteinemia has been recognized clinically. The present study was undertaken to determine if a simple method of estimating plasma proteins could be adapted to routine use in office obstetrics, while being sufficiently accurate to be clinically useful. Its application to a group of patients is described and discussed.

A short reference to the physiological and clinical aspects of the plasma proteins will first be made. Much of the evidence in the literature is of a conflicting nature, but certain assumptions appear to be reasonable.

Structure and Function of Plasma Proteins

The plasma proteins include albumin, globulins, and fibrinogen. The albumin fraction is clinically the most important protein in the plasma, maintaining osmotic pressure and viscosity. The globulins take part in antibody formation, and fibrinogen in blood clotting. It is unusual for either to be appreciably lowered in hypoproteinemia, which is always due to a depression of the albumin fraction.^{1, 2-14}

The plasma proteins are maintained either by an adequate intake of protein or when this is lacking, by the so-called reserve stores. These stores cannot be distinguished from the rest of body protein, but participate in the continuing metabolism of the individual. That they are located in the vital organs principally is suggested by the finding that during protein starvation, the liver, kidney, and alimentary tract rapidly give up 30 per cent to 40 per cent of their protein, while that within the muscle remains unchanged.¹⁵ However, as starvation proceeds, plasma¹⁶ and muscle proteins are called on to maintain these organs above their vital levels, and a decrease in the concentration of plasma proteins occurs.

Source of Plasma Proteins. The plasma proteins are synthesized within the body, from amino acids. The liver is the primary site of formation, but a secondary source, within the reticulo-endothelial system, is suggested to explain the occurrence of nutritional edema, in the presence of a normally functioning liver, adequate intake of protein, and positive nitrogen balance.¹⁷⁻²²

Causes of Hypoproteinemia.—Protein deficiency in the tissues is recognized, almost solely, by a decrease of protein in the blood, with a resulting loss of osmotic pressure. When the albumin fraction falls below 3 Gm. per 100 c.c. edema occurs.¹ Hypoproteinemia may be due to²:

1. *Excessive loss of plasma:* In addition to the plasma loss due to hemorrhage or burns, excessive exudation into the peritoneal cavity, or intestinal walls, occurs in peritonitis, ascites and acute obstruction.

2. *Faulty nutrition:* A lack of sufficient quantity or quality of protein in the diet, or improper absorption of an adequate intake results in hypoproteinemia.

^{*}Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Oct. 27-29, 1946.

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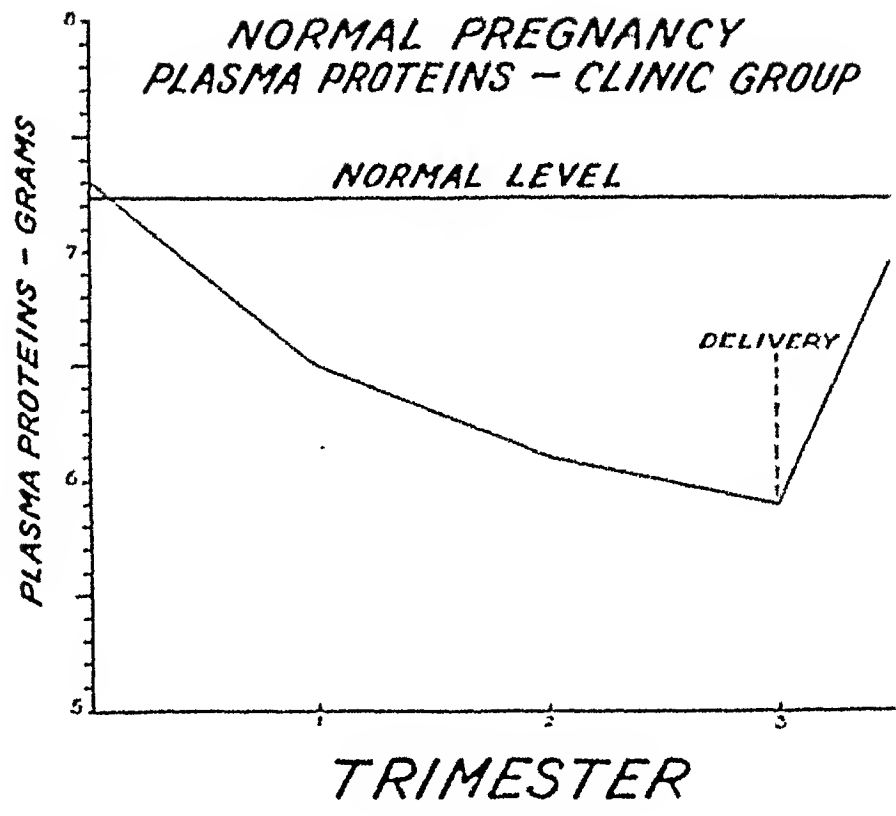


Fig. 1.

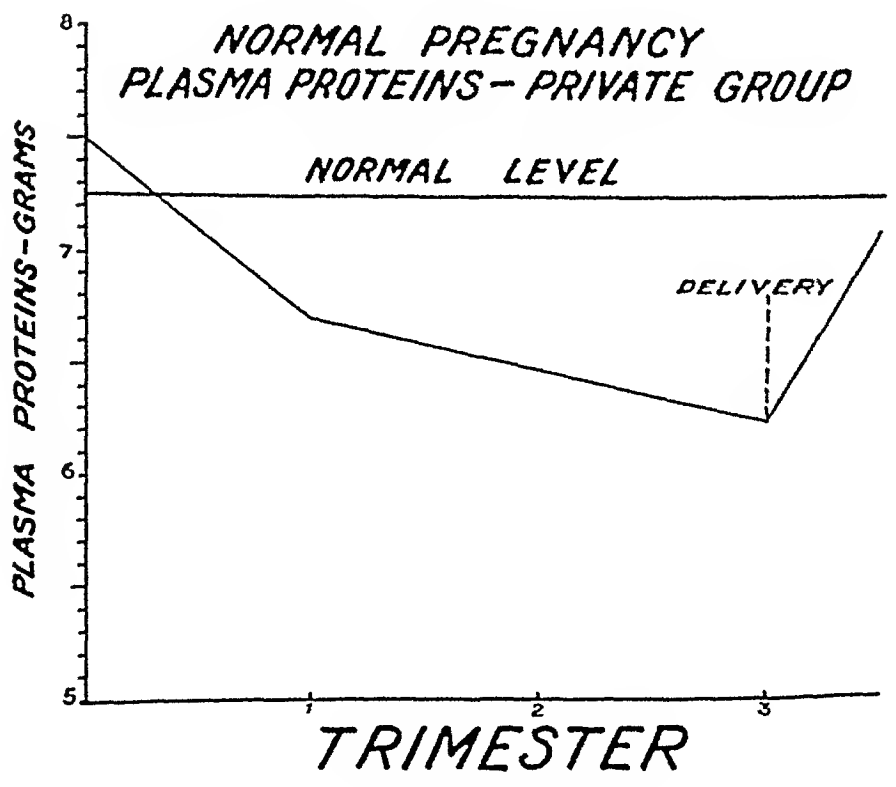


Fig. 2.

3. *Excessive loss of nitrogen:* Operations, various forms of trauma and general anesthesia, cause excessive destruction of protein, and a large amount of nitrogen is lost in the urine. In hyperthyroidism the loss is due to the increase of metabolism.

4. *Defect in synthesis:* Due to its important role in the production of albumin, liver insufficiency is accompanied by severe hypoproteinemia. The defect is not due to faulty nutrition because positive nitrogen balance can be maintained.

Replacement of Plasma Proteins

An adequate intake of biologically valuable protein will prevent hypoproteinemia.^{23, 26} If acute depletion has occurred, diet, intravenous amino acids, protein hydrolysates, or plasma will bring about restoration of normal plasma protein levels if used in sufficient quantities to maintain nitrogen equilibrium.²⁴ When depletion has been of long duration, plasma protein replacement, even with very high intake, may take months.²⁵ In cases of nephrotic and hepatic hypoalbuminemia, the restoration of normal plasma protein levels is notably ineffective.

Until recently, the diet of pregnant women was restricted in its protein content because it was thought to be toxic for the prospective mother. The observation that the patients who ate meat, eggs, and fish seemed to do better led to a study of plasma protein levels.²⁷ Hypoproteinemia was commonly found in pregnancy, and became extreme in toxic patients. It is now generally accepted that high protein intake in pregnancy will appreciably decrease the incidence of toxemia.²⁸

Simplified Method of Estimating Plasma Protein

Measurement of plasma protein concentration by Kjeldahl analysis is a highly technical procedure, and requires elaborate and expensive apparatus. For these reasons it is beyond the reach of the clinician. The use of gravity methods have failed to be satisfactory, until recently, because the organic liquids employed were highly volatile and explosive.²⁹ These difficulties have been overcome by the use of an aqueous solution of copper sulfate, which has a coefficient of thermal expansion almost identical with blood or plasma, and rapid protein coagulating power.

Compared with plasma protein determination by Kjeldahl analysis, the copper sulfate method has proved to be accurate to within ± 0.3 Gm. per 100 c.c.^{29, 30, 31} The stability of the solutions, the rapidity and simplicity of the test, make it ideal as an office procedure.

Blood is withdrawn from the superficial vein of the arm, and allowed to fall into solutions of copper sulfate of known specific gravity. Its behavior after the loss of initial momentum depends entirely upon its specific gravity as compared with the solution into which it has fallen. The ideal anticoagulant for this test has been shown to be heparin.

Application of Test.—The present study has been carried out on a total of 600 normal patients, and a small number with toxemia. The greatest number, totalling 450, were patients attending the prenatal clinic of the Catherine Booth Hospital, but a smaller number were studied in practice on the private maternity ward of the Montreal General Hospital.

Fig. 1 shows the average levels on the group of normal clinic patients. There is a steady fall throughout pregnancy with a rapid rise post partum; although clinically normal, these patients seem to show hypoproteinemia. An almost identical result was obtained with the private patients, even though one would expect a much higher level in this group whose income would allow a more expensive high protein diet (Fig. 2).

each patient. Plasma protein determinations were made at biweekly intervals. Over the three week period, no elevation of the plasma proteins occurred (Fig. 7).

The use of hydrolyzed protein in toxemia has been, of necessity, limited, through the lack of time imposed by the precarious condition of such patients,

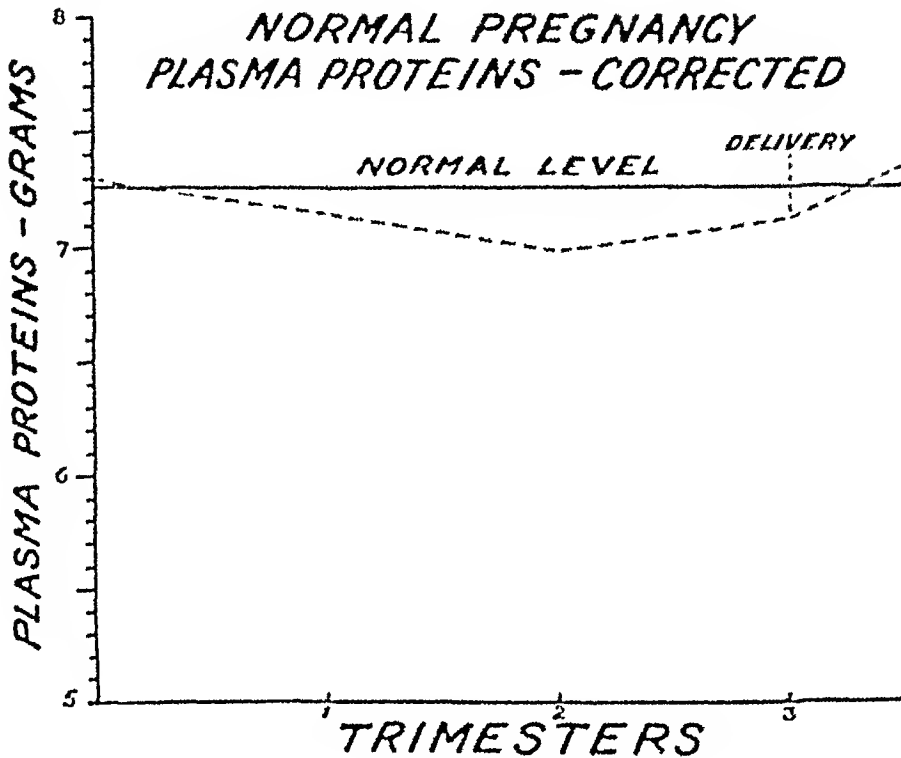


FIG. 4.

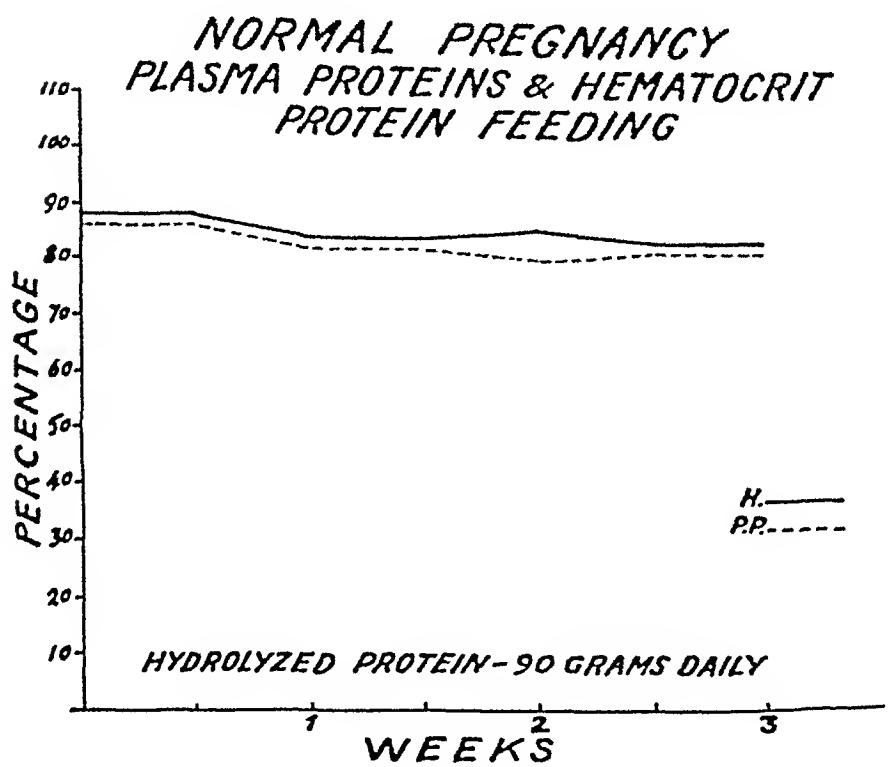


FIG. 5.

The similarity might be explained by the increased hydration of the blood during pregnancy. Hematocrit estimations will reflect changes in blood volume, and can be determined from the specific gravities of blood and plasma.^{32, 33}

When estimated in this manner, they were found to be consistently lower than those obtained by centrifuge, and more accurate as a measurement of the true cell volume within the circulation.³⁴

Protein and hematocrit levels expressed in terms of percentage are practically identical throughout pregnancy (Fig. 3). The hypoproteinemia coincides with the increased plasma volume, and to estimate the true level of plasma proteins the percentage of dilution should be added. Fig. 4, which represents such correction applied to our series of normal patients, shows the plasma proteins well within the normal range.

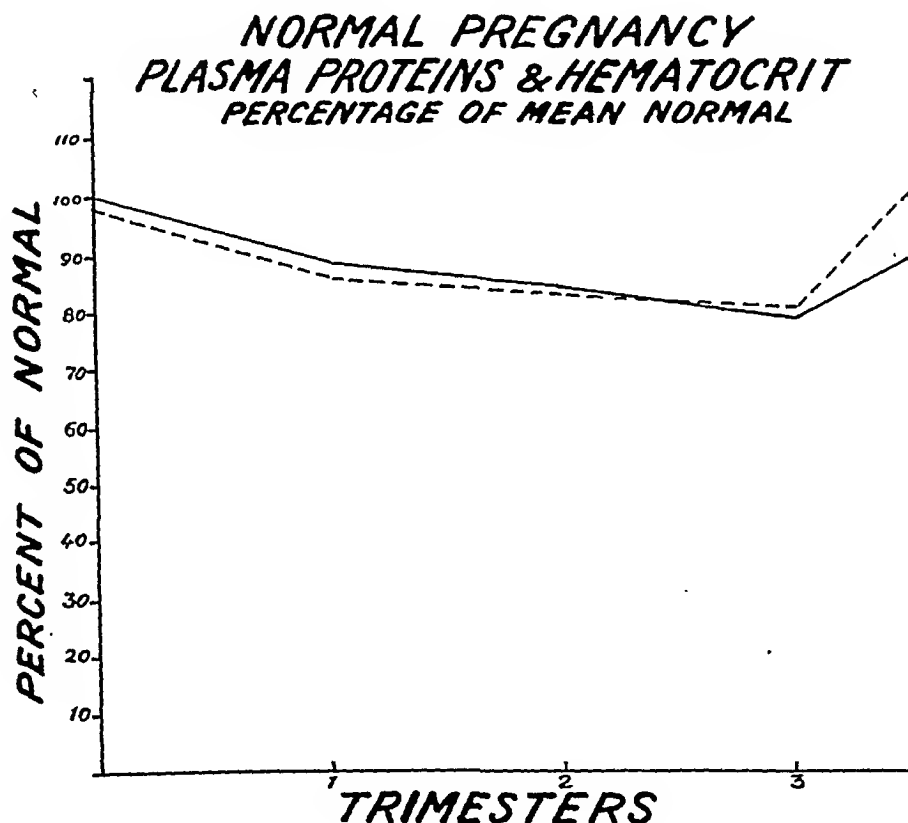


Fig. 3.

After correction for plasma dilution, such normal levels have not been present in the patients with toxemia. Figs. 5 and 6 show a marked difference between the hematocrit and plasma protein levels. In pre-eclampsia, a difference of 30 per cent was found, while in eclampsia the difference became more marked, as the hematocrit levels rose, and the plasma proteins fell. The relationship between hematocrit and protein levels may prove to be a valuable diagnostic aid in toxemias—an increase in difference between them is a poor prognostic sign, while a decrease in difference suggests improvement.

Protein Hydrolysates

During the course of this study, an attempt was made to evaluate the effects of supplementary feedings with protein hydrolysates by mouth and vein, in the normal patients and those with toxemia.

For this purpose, a group of twelve patients attending clinic were fed hydrolyzed protein over a period of three weeks, in the form of an enzymatic digest of casein. A daily supply of 100 Gm. of protein in this form was given

The response to oral hydrolysate supplements prenatally was observed in three cases of pre-eclampsia. In two of them, a daily supplement of 100 Gm. was given over a period of six days, while the third patient was given 200 Gm. daily for four days. No improvement was noted in edema, albuminuria, or plasma protein levels.

Similar observations were recorded when protein hydrolysates were given intravenously. With the preparation used, reactions were common, and included severe vomiting, abdominal pain, and flushing. They appeared when the rate of infusion exceeded $7\frac{1}{2}$ Gm. an hour, or when the preparation was not well diluted. Adequate dosage was difficult because it was necessary to limit fluid intake. Strict routine toxemic care was given simultaneously, so that interpretation of the results was difficult. The record of two patients is included.

One patient entered the hospital with a diagnosis of toxemia of pregnancy. She had gained 12 pounds in weight during a two-week period, with associated edema, and increase in blood pressure from a normal level of 120/70 to 150/100. The urine remained free of albumin. Her plasma proteins on admission were 3.9 Gm. Therapy included bed rest, sedation, a high protein, salt-poor diet, and intravenous protein hydrolysate, totalling 30 Gm. daily. No improvement resulted. Over a period of five days, plasma protein concentration decreased to 3.7 Gm., her weight increased 5 pounds, edema became more noticeable, blood pressure remained unchanged, and her urine output diminished. Premature separation of the placenta and still birth occurred.

Another patient was admitted with eclampsia. Convulsions were frequent, and only partial consciousness was regained between seizures. Her blood pressure was 160/110, almost complete anuria was present, and the albumin content was 10 Gm. per liter. Manifestly, no one should jeopardize the life of such a patient by relying on a measure not proved by clinical trial. Accordingly, morphia and magnesium sulfate were given, and Stroganoff's method of treatment was followed. An intravenous injection of glucose and hydrolyzed protein was administered. Convulsions ceased shortly after treatment was started, and did not recur. A rapid fall in blood pressure, increase in output of urine, and decrease in albumin were noted. Over the next four days, a daily intravenous of 60 to 90 Gm. of protein was given. Reactions were marked but not alarming. The fetal heart sounds disappeared on the second day, and on the fourth day spontaneous labor terminated with the expulsion of a stillborn baby, followed by a prematurely separated placenta. The plasma proteins on admission were 3.98 Gm., and 3.7 Gm. at the time of delivery.

Methionine.—Methionine was administered to a single patient in this study. The patient was admitted to hospital with pre-eclampsia. She had first been seen in February, 1946, and her expected date of confinement was October 3. She was examined at monthly intervals and, previous to Aug. 22, 1946, her weight had increased from 150 to 174 pounds only. Her blood pressure had remained low, around 110/160, and there had been no albumin found in the urine. On this day, Aug. 22, 1946, however, she was found to be very edematous, her weight had increased in one month from 174 to 195 pounds, and the blood pressure was 185/110. The urine contained an abundance of albumin. She had no complaints, and the fetal heart tones were normal. She was admitted to the hospital on the following day, where her weight was recorded at 196 pounds, albumin 4 Gm. per liter, plasma proteins were 4.35 Gm., and blood pressure 180/120. A high protein, salt-poor diet was ordered, along with complete bed rest, phenobarbital twice daily, magnesium sulfate by mouth to induce watery stools, and oral hydrolyzed proetin to tolerance.

who usually must have their pregnancy terminated soon after admission to the hospital. In our experience, the plasma proteins rise rapidly post partum in both the normal and toxic patient, and they have not been included.

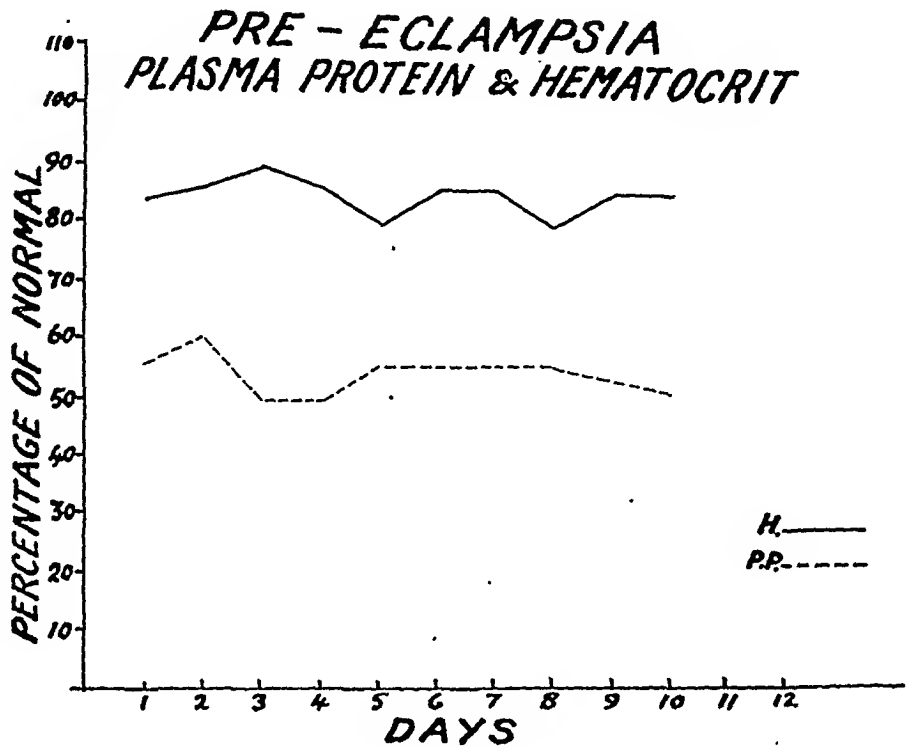


Fig. 6.

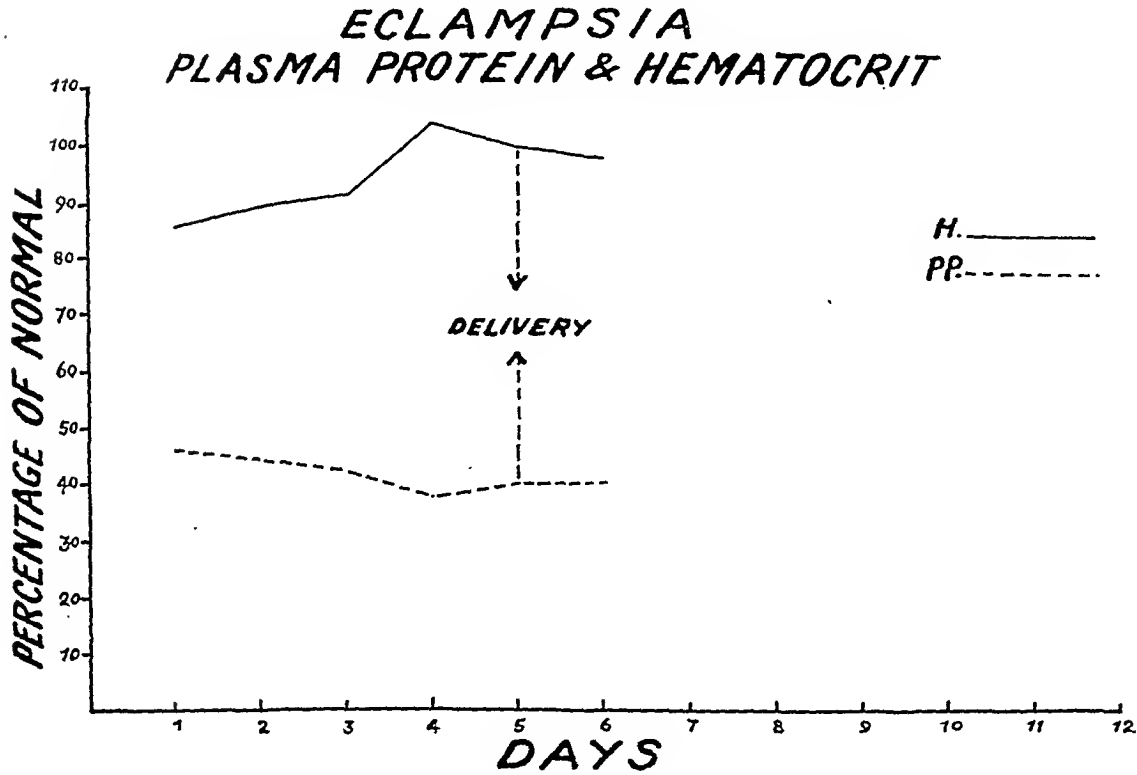


Fig. 7.

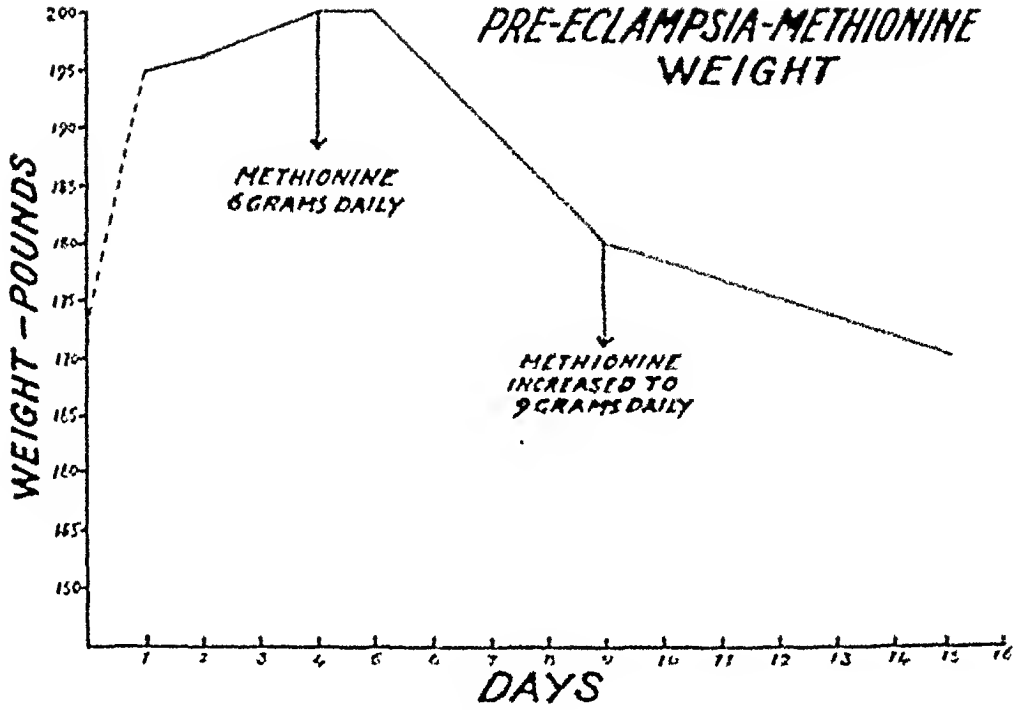


Fig. 10.

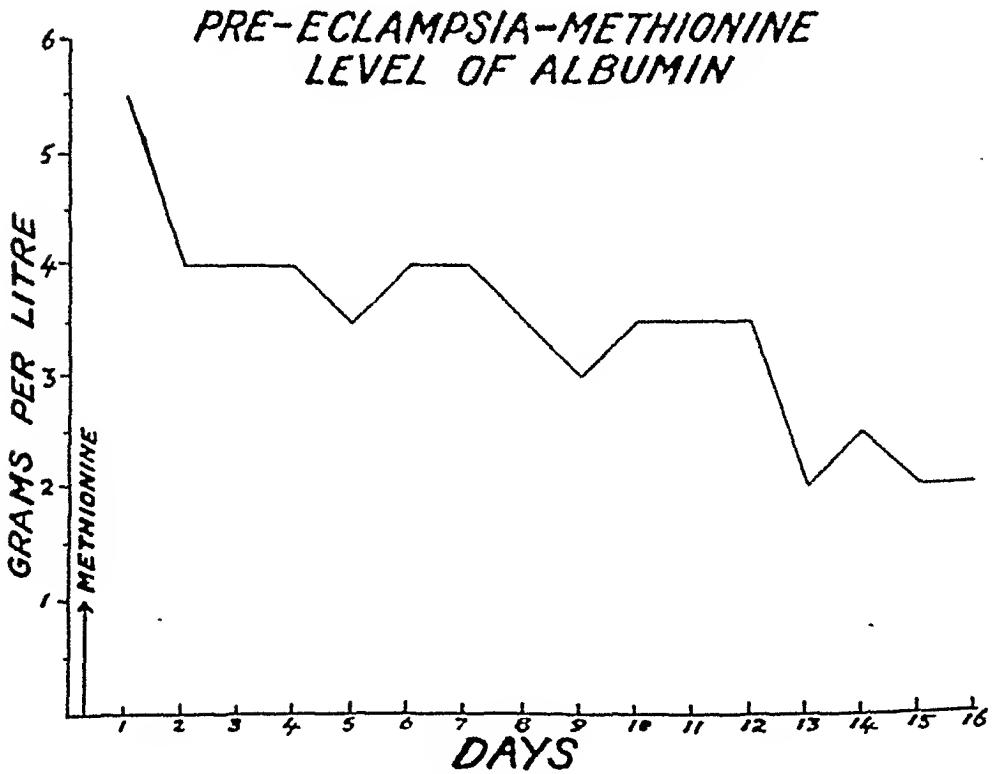


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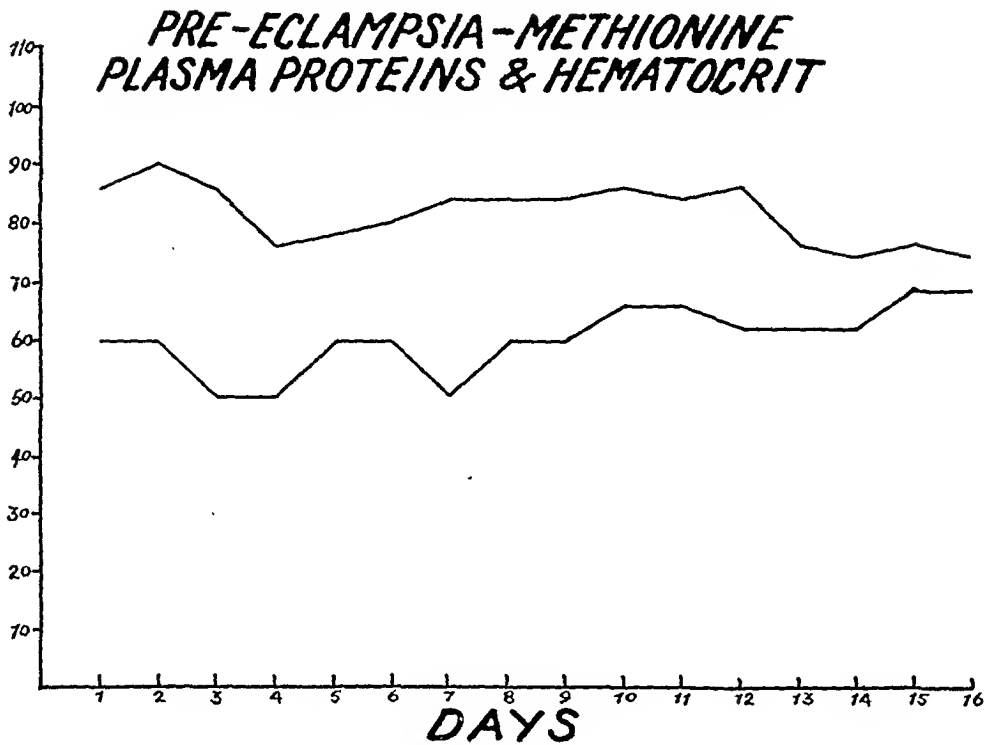


Fig. 8.

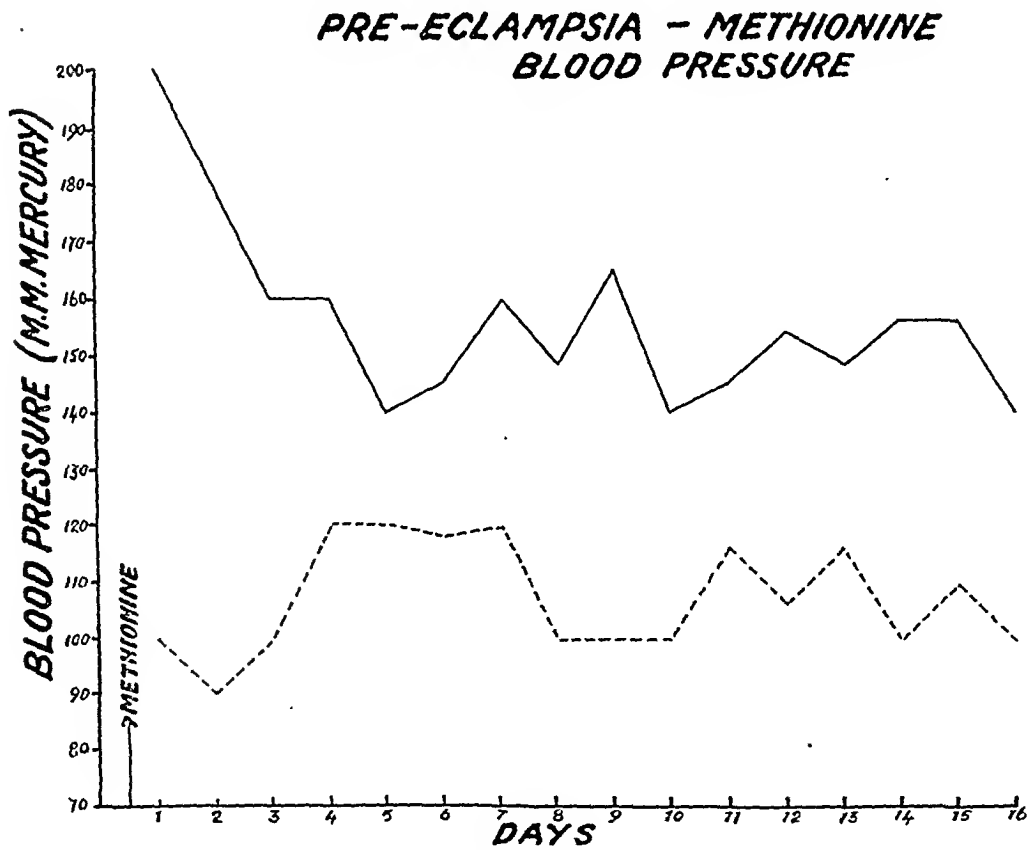


Fig. 9.

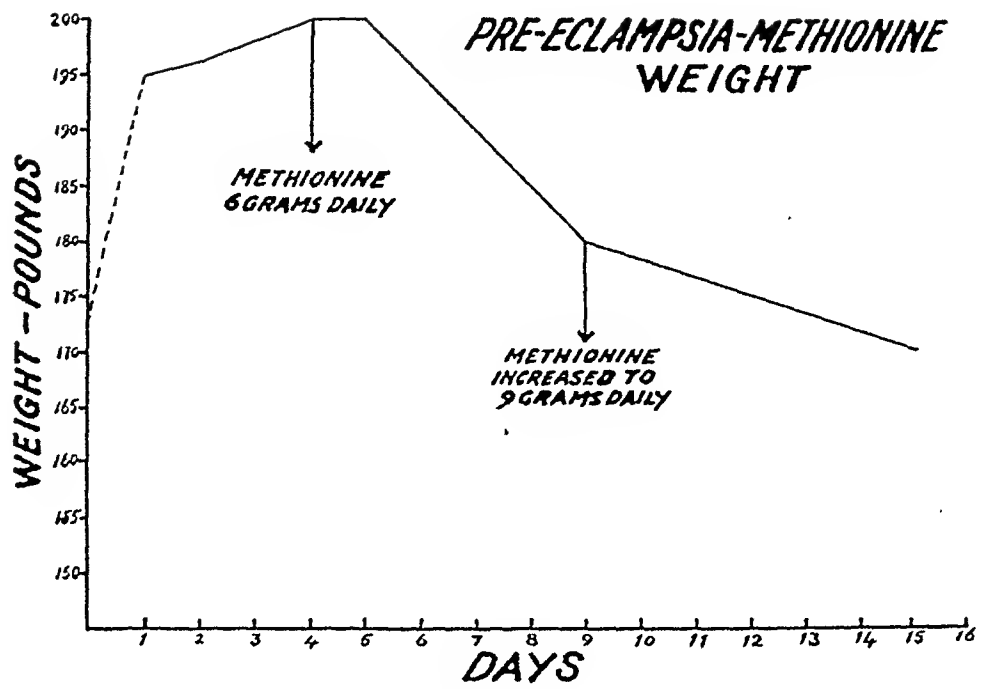


Fig. 10.

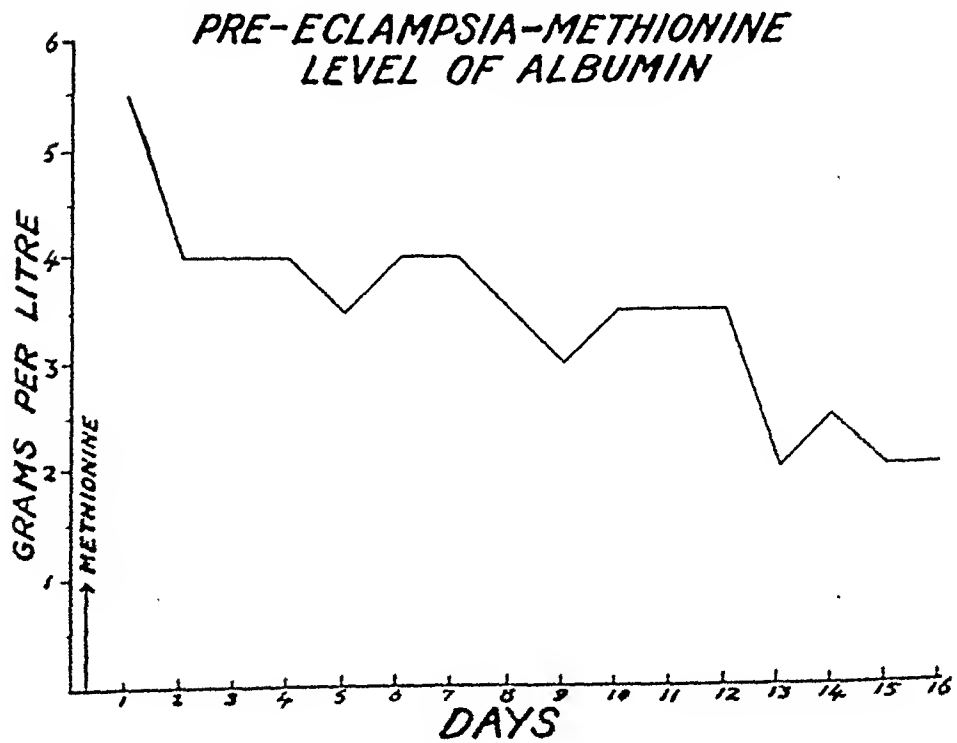


Fig. 11.

During the following four days no improvement was observed. On August 27 her blood pressure was 200/130, weight 198 pounds, and albumin $5\frac{1}{2}$ Gm. per liter. The fetal heart tones were normal, but the baby was estimated to be less than 4 pounds. The plasma proteins were 4.25 Gm. per 100 c.c. The urinary output averaged 1,000 c.c. daily.

The hydrolyzed protein was discontinued, and methionine was started, with a daily total dose of 6 Gm. being given by mouth. No other change was made in treatment. During the following twenty-four hours marked diuresis began (Fig. 8) and was accompanied by a steady fall in weight (Fig. 9). The blood pressure did not appear to be affected (Fig. 10). The level of albumin steadily decreased during the course of treatment (Fig. 11). Condition of the mother was excellent clinically, and the fetal heart tones remained regular. The day preceding labor her weight was $171\frac{1}{2}$ pounds, a total loss in two and one-half weeks of $26\frac{1}{2}$ pounds; urinary output was 2,540 c.c.; blood pressure average 160/100, and albumin $2\frac{1}{2}$ Gm. per liter. The plasma proteins showed a gradual, although slight rise to over 5 Gm., and approached the hematocrit levels. Labor was normal, and a living $4\frac{3}{4}$ pound baby was delivered.

Methods of Supplying Proteins

The use of protein feeding by mouth should be regarded as of major importance. The use of hydrolyzed or predigested protein, orally and intravenously, is becoming popular. A third method, still largely experimental, is the ingestion of certain amino acid components of protein. Evidence produced in animals supports the hope that methionine especially may be proved to be specific in protecting the liver against the ill-effects of protein starvation, or toxic substances.

The ideal diet in pregnancy must fulfill certain requirements. It must furnish protein in biologically valuable form; it must allow such protein to be used by the body for the optimum construction of the fetus, and replacement of wear and tear tissue in the mother; it must be sufficient to allay hunger; it should, if possible, be acceptable to the patient.

Protein itself, unless protected adequately within the body, will be largely broken down and used as a source of energy. When large amounts are given intravenously, approximately 50 per cent is deaminized and used as a source of calories.³⁵ Several dietary factors conserve nitrogen within the body and prevent such breakdown. If protein intake is high, a sufficient portion will be spared to supply the patient's needs, but, being expensive, cannot be taken in such quantities by the less fortunate group of patients. Furthermore, excessively high protein diets are not well tolerated by many people.

Protein of high biologic value, such as meat, milk, and eggs, is more readily retained. In this sense, vegetable protein is a sparing substance, too, in that it will be deaminized by the body before the more valuable animal protein. This "protein protection of protein" probably explains the good health maintained by people who live on the so-called vegetarian diet.

A third and very important factor is the protein sparing value of carbohydrates, which enhance the storage of nitrogen within the body.³⁶ Furthermore, the time of ingestion of carbohydrates must be emphasized, for they exert their greatest protein-sparing action only when they are available during the period that the intensity of protein metabolism is at its maximum.^{37, 38, 39} This interval is limited to within four hours of ingestion of the regular meal.

Positive nitrogen balance can be maintained by the use of a high carbohydrate, low fat, high protein diet, even with low caloric intake, by the simple maneuver of saving 20 Gm. of carbohydrate from each of the three main meals, and feeding this portion in the midmorning, midafternoon, and evening.³⁷ There is relief from midmeal hunger, and the decreased physical efficiency seen when the stomach is empty.

Hydrolyzed protein may be administered as a supplement prophylactically, or as a temporary therapy, when digestion or absorption is impaired. Our experiences in this study have left doubt as to the value of such substances in pregnancy. The daily ingestion of large quantities caused no increase in the concentration of plasma proteins over a period of three weeks. It may be assumed that the levels in the normal patients were due to hydration of the blood, the patient was not truly depleted of protein, and therefore added feedings were not necessary. If such an assumption is false, the only other conclusion tenable is that these patients are chronically hypoproteinemic, and prolonged feedings over months would be necessary to increase plasma protein concentration. Hydrolyzed protein is far too expensive to be used in this manner in practice.

No pre-eclamptic patient so treated in this study responded clinically, or had an increase in the concentration of proteins in the plasma before delivery became imperative. Although the patient with eclampsia improved rapidly, she was under strict eclamptic regime with sedatives, and death of the fetus was not prevented.

Methionine is one of the essential amino-acids. It is closely related to cystine and both are sulfur containing. Feedings of cystine-choline or methionine mixtures exert a beneficial change upon a damaged liver.⁴⁰

Liver necrosis, similar to that seen in human eclampsia, can be produced in animals by protein starvation.⁴⁰ Such experimental dietary hepatic injury is often combined with bilateral hemorrhagic cortical necrosis of the kidney, seen in human beings only during pregnancy.⁴¹ Both can be universally prevented by the ingestion of protein with high methionine content such as serum albumin, casein, and egg white.

In rats who had developed ascites on a protein deficient diet, a reversal of the condition was obtained by feeding methionine. The first change observed when such therapy was instituted, was marked diuresis similar to that noted in our case.⁴⁰

In pre-eclampsia and eclampsia, several investigators have studied the function of the liver, and have produced evidence to show that impairment exists.⁴²⁻⁵² The toxic hepatitis produced by carbon tetrachloride and chloroform⁴² has been benefited in both animals and human beings by the administration of methionine.^{53, 54, 55}

Prevention of hepatic injury in human beings requires a daily intake of from 2 to 4 Gm. of methionine or a protein rich diet with a high methionine content.⁴⁰ Limitation of fat is essential since it has been shown to aggravate hepatic injury and to prevent the metabolism of protein.

Although experience with methionine in this study has been limited, the observed dramatic changes in weight, edema, and clinical improvement, after five days on usual pre-eclamptic routine had failed, suggest that the results in animal experiments may be hoped for in human subjects. We chose the oral route of administration because it seemed more likely to concentrate the methionine in the liver by way of the portal circulation. Quicker results appear likely when the substance is used intravenously.⁴⁴

Summary

A study of plasma proteins by means of the copper sulfate test upon 600 patients during pregnancy is presented. The effect on plasma protein levels and clinical condition by feedings of protein hydrolysates, and methionine is recorded.

Conclusions

1. The copper sulfate method for measuring the specific gravity of the blood serum or plasma gives satisfactory and clinically accurate estimations of plasma protein concentrations. It is simple, quick, and may readily be carried out as an office procedure.

2. Combined hematocrit and plasma protein estimations give more information than the plasma proteins alone.

3. The hypoproteinemia of normal pregnancy is relative to plasma dilution.

4. Over short periods of time, feeding of hydrolyzed protein by mouth or vein produces no elevation of plasma proteins, or improvement in the clinical condition of patients with toxemia of pregnancy.

5. The hypoproteinemia of pre-eclampsia and eclampsia is very likely due to failure of albumin synthesis by a damaged liver.

6. The essential amino acid-methionine, may, by its protective action upon the liver, materially aid in the prevention and treatment of toxemias of pregnancy. Further experience with its use is necessary.

I would like to express my appreciation to Drs. Paul Guorgy, A. D. Campbell, N. W. Philpott, and J. S. L. Brown for their criticism and help. The oral hydrolysate used was supplied by Frank W. Horner, Inc., the intravenous hydrolysate by Frederick Stearns & Co., and the methionine by Ayerst, McKenna, and Harrison.

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Discussion

DR. CANNELL.—Dr. Macarthur has presented results of a very interesting and careful study of plasma proteins in 600 patients. His findings are corroborated in general by many other investigators. To me the principal value of his work is that he has drawn our attention to a simple and accurate method of estimating plasma protein which he tells me, and other biochemists have told me, is quite capable of use as an office procedure. Dr. Macarthur has shown by his paper that this procedure is a useful one which can be adapted to office practice. I feel that anything which will add to our accurate treatment of patients during pregnancy is something that should be drawn to general attention, and he has done that.

From his paper I was not clear whether the relationship between the hematocrit and plasma protein levels preceded the clinical changes which we know as pre-eclampsia, i.e., elevation of pressure, edema, and the other signs. I hope that Dr. Macarthur will clear this up for us. If these findings are found to precede clinical signs by any appreciable time, it is a much more valuable procedure than just an aid in the dietary care of a patient.

He stated earlier that the changes in the liver which are produced by protein starvation are the same or similar to those encountered in the patient dying from eclampsia. I cannot agree that there is any typical picture of eclampsia in a large series of cases. I think that probably about 50 per cent is the maximum number of patients who will show the changes in the liver said to be typical of eclampsia. He has told me that he does not feel that that is of importance in any case, because he is not trying to advance a theory for the cause of eclampsia, but noted that in patients who had a poor protein intake these changes could be induced more readily.

In conclusion, I would like to congratulate Dr. Macarthur on a very excellent presentation, and would urge him to proceed with his studies, particularly with respect to methionine, as it is very interesting.

DR. VAN WYCK.—I believe that thirty years ago it was pointed out that in analyzing the behavior of the serum protein fractions in pregnancy, the shift in the relationship of albumin and globulin was very marked in the toxemias. This was a diagnostic point in the differentiation of eclamptic toxemia from other forms of renal disease in pregnancy. Some years ago Harding noted that in early pregnancy, when the ovum is acting to some extent as a parasite, there was a fall in the serum protein due to the physiologic hydremia,

but that when the patient developed hyperemesis gravidarum, the serum proteins were concentrated, the total figures rising sometimes to 9 per cent, this rise being the measure of acute dehydration. With prompt treatment in an attempt to restore the water balance, the serum protein figures fell back below the prepregnant level as the patient recovered. Harding pointed out, however, that closely recurring attacks of dehydration produced a destruction of these blood substances due to the effort the body made in the contracted and concentrated blood volume to restore the changed viscosity. At first a rapid rise in serum protein followed by a fall and then a rise with a further attack of dehydration, and then a recurrent repetition of this phenomenon ultimately resulted in a low fixed blood protein. Harding regarded this ultimate fixation of the serum protein as a bad prognostic finding. The strange behavior of plasma proteins in pregnancy is now the subject of much investigation, and promises much in the understanding and therapy of toxemia.

DR. EDWIN ROBERTSON.—The point which I should like to hear discussed is one which has not already been mentioned, namely, the specific nature of the toxemia of pregnancy. I am referring to the work of the Smiths in Boston who, some time ago, discovered a toxic factor. The Smiths thought it possible that there must be something in the folklore which points to menstrual discharge being poisonous; they found a highly toxic pseudoglobulin in menstrual discharge similar to that which Menkin had isolated in turpentine-produced pleural effusion in dogs. They also found such a toxic factor in the blood of women suffering from toxemia.

I wonder whether, in his study of toxemia, Dr. MacArthur has taken cognizance of the Smiths' work on the subject.

DR. PHILPOTT.—I believe that perhaps the most important contribution that will be made in the treatment of toxemia and eclampsia might be in this direction. We do not know much about the causation of toxemia today, but we struggle with many causes. There is a very definite relationship between toxemia and low plasma protein. We have had in the last two years several cases that have responded very well to different forms of supplementary protein administration. One case under study had a very low plasma protein, 3 Gm. per cent, and was treated with plasma transfusion. Three transfusions of 250 c.c. each were given in four days. At the time of her first transfusion blood pressure was 200, eyes were almost closed with edema, and the patient looked as though she were head for a convulsion. With the first transfusion the symptoms started to disappear, and with the third she was normal with reference to the edema and blood pressure. The patient was carried along for some time and she was delivered a few weeks later of a normal baby. She showed no sign of toxemia at the time of delivery.

I believe there is a great future with Methionine. It is used in our clinic for post-operative cases in shock and has been managed by Dr. Browne with excellent results. We find it a most beneficial way of treating cases of suspected or definite liver damage.

DR. MACARTHUR (Closing).—In reply to Dr. Cannell, I must say that we have as yet not established the value of the hematocrit-plasma protein test in the early, sub-clinical, toxic woman. The source of my impression regarding hypoproteinemia is mainly the work of Guorgy, who has shown that prolonged protein starvation in animals causes necrosis of the liver identical to that found in human eclamptics, often combined with bilateral cortical necrosis of the kidney.

We have not used plasma in the treatment of toxemia, chiefly because it is difficult to obtain, and protein hydrolysates are much cheaper, although perhaps not as physiologic.

I freely admit, with Dr. Robertson, that many interesting hormonal theories have been elaborated, to explain pre-eclampsia and eclampsia. Liver damage may not explain this complex disease, but may be an important link in the chain. Perhaps by its adequate protection we may go far in finding the solution.

I would refer Dr. Puddicobe to the articles of Phillips and others in which they give the complete technical details of plasma protein, serum protein, hematocrit and hemoglobin, and red cell counts. Their directions are sufficient to enable anyone to carry out this test in the office.

If excessive blood is lost, it should be replaced as soon as possible and in sufficiently large amounts. Blood is the puerperal woman's most powerful ally but if not immediately available, plasma is now procurable in even all outlying districts. We have become aware of its lifesaving qualities in cases of shock, yet more and more it becomes apparent that plasma will not save life if the blood loss has been great. Some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. If veins cannot be entered, bone marrow infusion through the sternum is a procedure which should be used.

According to the statistics of the Chicago Lying-in Hospital, heart disease has been one of the major causes of maternal death. Our Canadian statistics of maternal death do not list death from cardiac disease. The rate of mortality from phlegmasia alba dolens, embolism, or sudden death does not run a parallel course with sepsis. An almost steady rise occurred since 1934, ending with a definite peak in 1940 with 156 deaths. The rates for all other conditions except accidents were the lowest in that year. The rate in 1944, however, was the lowest ever recorded—seventy-six deaths.

Under the heading of other accidents of childbirth are included cesarean operations, other surgical operations, instrumental deliveries, dystocias, ruptures of the uterus in parturition, together with other or unspecified conditions of the puerperal state, as puerperal diseases of the breast, etc. In 1940, ninety-nine deaths were attributed to these causes, which was 8.3 per cent. Since 1936 there has been a steady decrease in these numbers. The use of blood and plasma has decreased the number of fatalities from cesarean section. The careful selection of cases, improved preparation, better methods of anesthesia, and the lower uterine segment type of operation has made it a safer procedure.

The prevention of maternal mortality should begin in childhood. In the prevention of rickets, tuberculosis, syphilis, and the acute communicable diseases of childhood, we are laying the foundations for a healthier motherhood. The growth and normal development of girls are dependent largely upon proper nutrition, freedom from infections, and suitable exercise. It is well known that rachitic pelvis, damaged hearts and kidneys, and chronic foci of infection increase the risks of pregnancy. Health should be regarded as a major objective of modern education. In all secondary schools ample provision should be made for mothercraft classes to be instructed by well-trained and experienced public health nurses. These should be made compulsory for all girls. They would be better equipped for motherhood, would also have a fund of knowledge which would help them to meet the broader problems of social hygiene. Another important factor in the reduction of maternal mortality is the puerperal woman herself. The ability to choose a skillful physician, a competent nurse, and a well-equipped hospital are of vital importance. Her capacity to grasp and to carry out simple hygienic rules and her "teachability" as to the importance of symptoms and signs, which indicate approaching danger, are large factors.

A well worked-out program of parental education should be available in every community in which parent-teacher associations, women's clubs, etc., should be encouraged to take an active part. Prospective mothers of all grades of

The promise of still greater improvement will depend upon close supervision of all pregnant women, and the earliest possible recognition of the actual appearance of toxemia. The causes of the toxemia of pregnancy are still unknown, and the prophylaxis is still better than cure. Good prenatal care, increased hospitalization of pregnant women, and prompt institution of bed-rest treatment of even the mildest case of toxemia will give us improvement. Prevention of the occurrence of eclampsia in a nonconvulsive toxemic patient by proper medical management is of paramount importance. The mortality of the convulsive toxemias is eighty times as great as the noneconvulsives.

The accuracy and value of statistical deduction depend upon the quality of the information furnished by the certificate of death. The figures for 1941 to 1944 were compiled according to the fifth revision of the *International List of Causes of Death* and are not strictly comparable with the figures for 1940 for individual causes. Obstetric death is commonly the result of several causes, rarely one, and actually it is very often impossible to assign death to one cause.

It has been said for many years that infection as the most common cause of maternal death is the most important. Hemorrhage is no doubt far more common everywhere than indicated by its statistical frequency, and it is the outstanding controllable factor. Preventive measures for reduction in maternal mortality will produce greater results if we place emphasis on hemorrhage rather than infection. At present hemorrhage is the most important cause of maternal mortality, and probably the most common as well. In a study of the Maternal mortality statistics of the United States for 1941 and 1942, it was found that in 1942 there was a 10 per cent reduction in the deaths due to infection, an 11 per cent reduction in deaths from toxemia, but practically no decrease in the number of deaths from hemorrhage. In Canada there has been little, if any, improvement in maternal mortality from hemorrhage since 1931, when there were 137 deaths from hemorrhage. In 1940, maternal deaths from hemorrhage numbered 138, comprising 14.1 per cent of all maternal deaths. In 1942 there were 155, comprising 17.2 per cent. In 1943 there were 170 deaths from hemorrhage. In fact, hemorrhage was the largest single cause of maternal mortality, 21.3 per cent.

Undue loss of blood is to a great extent preventable. Hospitalization of every woman who bleeds during her pregnancy, and routine blood studies with blood typing and the determination of the Rh factor are essential. Many of the obstetric complications are influenced by hemorrhage. In the early months of pregnancy ectopic gestation and abortions are the chief causes. Later in pregnancy placenta previa and abruptio placentae cause the serious hemorrhages. In the delivery, trauma and the placental stage are the main causes of death from hemorrhage.

Proper conduct of the second stage of labor and conservative management of the third stage will reduce materially the deaths which are directly due to hemorrhage, and will also enable the puerperal woman to combat complications, particularly infection and toxemia, which might otherwise prove fatal.

If excessive blood is lost, it should be replaced as soon as possible and in sufficiently large amounts. Blood is the puerperal woman's most powerful ally but if not immediately available, plasma is now procurable in even all outlying districts. We have become aware of its lifesaving qualities in cases of shock, yet more and more it becomes apparent that plasma will not save life if the blood loss has been great. Some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. If veins cannot be entered, bone marrow infusion through the sternum is a procedure which should be used.

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A well worked-out program of parental education should be available in every community in which parent-teacher associations, women's clubs, etc., should be encouraged to take an active part. Prospective mothers of all grades of

intelligence and of all social classes will take advantage of instruction for expectant mothers, if presented by thoroughly trained and experienced public health nurses.

This instruction should be made available to all prospective mothers and fathers, regardless of their economic condition.

If 85 per cent of the maternal deaths are preventable as one obstetric authority states, the time is ripe for action. Judging by accomplishment in other fields, a "*Canadian Safe Motherhood Association*" or some such name would serve to crystallize the energy awaiting leadership. Obstetric authorities are prepared to give expert advice; public health workers are accustomed to organize and promote, and the informed public will furnish the financial support.

Medical and hospital care should be supplemented by education of the public, through the work of public health nurses, the press, radio, and other media, regarding the need for, and value of, good maternity care. The public should be instructed as to the proper diet and hygiene for the mother during the maternity cycle. There can be no question that well-equipped maternity hospitals with skilled staffs, using conservative methods of treatment, are the safest places in which to have a baby. In Canada, one of our great needs is increased hospital accommodation. It is estimated that only 47 per cent of pregnant women in Canada are able to be delivered in hospitals. To assure maintenance of adequate hospital maternity services in any community, hospitals must not be dependent upon charity contributions and upon the extra charges of private patients to meet the loss through its free services. Any approved hospital should be supported from public funds on a cost basis for providing all in-patients maternity care, the cost of maintenance of facilities for the prenatal care and all laboratory and x-ray services. The maternity patient administration is a community responsibility, and a larger provision should be made from public funds.

We do want to have the best maternity care for all mothers that it is possible to provide, so that Canada will be a place of safe motherhood.

Discussion

DR. PHILPOTT, Montreal.—Dr. Kerr has shown very ably today that hemorrhage is the greatest killer, and that it is preventable. We shall prevent it only by comparing results in various clinics. I would like to exchange statistics with Toronto, Winnipeg, and Vancouver. We could learn a great deal.

I am sure that in our clinic (Victoria Hospital of Montreal) today half of our patients who die could have been saved had they had adequate treatment. In a society such as this we could go forward in a concentrated effort to organize the management of obstetric patients. We should have some system and recommendations to offer to general practitioners and the public whereby each individual doctor will fit into his proper place. I think, as Dr. Sanche said, that many general practitioners do not have the right facilities, and specialists are at a disadvantage in having to handle patients that are tragedies before they see them. A plan whereby general practitioners would handle certain types of cases, others to be handled by specialists, and still others handled in hospitals would be advisable. It is the obligation of this society to make this endeavor.

DR. HECTOR SANCHE.—This ten-year analysis of maternal mortality in Canada is of pre-eminent interest, and the steady improvement it has shown, improvement which goes on in 1945, whose maternal death rate has been 2.3, is an encouragement to the medical profession.

Although there is a considerable improvement as a whole, each of the eleven headings under which deaths from puerperal causes are classified do not mark great percentage changes in regard to the total.

The three chief causes of maternal deaths are always septicemia, toxemia, and hemorrhage, and in the order stated; they stand for 70 to 75 per cent of all deaths. Septicemia has kept approximately its same percentage, toxemia has improved, while hemorrhage has increased.

Dr. Kerr has stated as factors of improvement: better hospital facilities, increased desire on the part of patients to seek hospitalization, improved obstetric technique, prenatal services, use of plasma, sulfonamides and penicillin, and has emphasized the development of these factors to a higher level.

Three parties are interested in the improvement of the maternal death rate: the medical profession, the patient, and the public. All three must cooperate if we want to get better results.

I can say that the medical profession as a whole is always looking for better standards in medical care. But we cannot bring for comparison specialists who work in favorable conditions, who are ready and able to improve their obstetric technique, and the general practitioner.

All hospitals will tell us that their maternal death rate is brought higher than it should be, not from their booked cases, but from their emergency cases. What does this mean? That the medical care is not of the same standard inside and abroad. And why? Because the factors mentioned above are not found at the same level here and there.

If we want to keep on the downward grade of the maternal death rate, we must continue the work in hospitals, but we must also help the general practitioner and enable him to share the benefit of our work, both in researches and facilities.

Most of us are teachers in our different communities, and we are aware of what our students know when they leave the University. They are well enough equipped to look after normal obstetric cases, but how many eclamptic patients have they seen, how can they handle a case of dystocia? And I would add, when will they be able to handle these properly if we admit that they attend fifty to sixty maternity cases a year, and when we know that severe dystocia or pathologic cases are sent to a far-off hospital where they cannot be associated with the delivery, and perhaps hear about the treatment only by the patient's own report.

The patient's cooperation consists in having her come to the doctor's office or to the clinic for medical supervision first, and second, in having her convinced of the importance of the directions she is given.

The increased desire on the part of patients to seek hospitalization is actually curtailed by the hospital facilities. Live births in institutions have increased from 39 to 60.9 between 1938 and 1944, and this increased demand has created shortage of hospital beds. On the other hand, when birth in an institution is mentioned, "institution" does not necessarily mean a well equipped hospital.

We should also bear in mind that 90 of 798 mothers died in 1943 without having a doctor in attendance, that is 11.3 per cent. This fact may come from two causes: (a) neglect on the part of the patient, (b) scarcity of doctors.

The cooperation on the part of the second party will be obtained inasmuch as the third party, the public, is aware that pregnancy is a matter that should be prepared and looked after, and that it is now recognized that prenatal hygiene, prophylaxis, and medical attendance will save many mothers' lives.

And here I agree with Dr. Kerr's recommendations that the prevention of maternal mortality should begin in childhood, that parental education, and that the education of the public should be done through the press, radio, and all other possible media.

Well-equipped maternity hospitals with a skilled staff is surely the safest place to have a baby. These hospitals should be disseminated on a larger scale in different centers throughout the country, so that one of them be within easy reach of every practitioner. There the isolated medical man in the country could take his patient to get treatment, if necessary, or to seek advice from a skilled specialist for further treatment at home, without having to lose days of his own time.

Before closing this discussion, I would like to set forth an idea. It is timely to discuss maternal mortality. It has been said that 85 per cent of maternal deaths are preventable; I agree, and they would be prevented if—but there will always be so many ifs—that, it is my opinion, the maternal mortality rate is not likely to come down a great deal more. This is no reason to give up in despair.

But it would be of paramount importance to take more interest in maternal morbidity (morbidity during the puerperium) and permanent invalidity to any degree. So many mothers are crippled, I dare say, to a certain extent after one or several pregnancies. Would it be possible to have a uniform base of obstetric morbidity all over the country, to establish statistics in this regard? In this way we could see the end results of our obstetric work, not only inasmuch as those who die, but inasmuch as they live and go through pregnancies curtailed in health, in their vitality, and in their potential in regard to themselves, their family, and the nation.

And I believe that this society comprised of obstetricians and gynecologists is the organization that should set forth this idea throughout Canada.

DR. FRASER.—There are one or two points I would like to bring up. Dr. Kerr has very ably presented the picture as it exists in Canada and elsewhere. I have always had the feeling that one of the greatest weaknesses of our present system lies in our failure to provide the average pregnant woman with the same type of treatment and care that we give the prospective surgical patient. Over the years there has been developed widely a place for the preparation of a woman for operation. Nothing is considered extravagant in the way of examination of treatment prior to the event, yet the average pregnant woman who is about to undergo a surgical procedure receives very scanty consideration. Often a woman approaches delivery with a hemoglobin of 50 to 60 per cent—sometimes less, far below the level considered necessary for a surgical operation. It is possible and should be regarded as essential that the hemoglobin level in pregnancy be maintained at or near 100 per cent. *What then is required is the provision for each and every pregnant woman of a sound and complete medical examination?*

In the report of the *British Committee on Maternal Mortality* tabled in the House of Commons in 1932, in which a very large series of Maternal deaths were analyzed, it was possible to recognize two large groups of cases: (1) those where death was due to childbirth, directly; (2) those where death was indirectly due to childbirth. In group 1 sepsis played a leading role. It was shown that the occurrence of sepsis over the previous hundred years displayed about the same incidence. Reports from Ottawa show the high incidence of sepsis in the causation of death from childbirth. I wonder if we are convinced of the importance of nasopharyngeal infection (active or latent) in those in attendance on pregnant women? Colebrook and his group in London have shown clearly the possibility of transmission of infection from this source and, indeed, have been able to trace the source of infection in many cases to this region. *Sporadic outbreaks* of infection in maternity hospitals may in this way be explained. It is essential that women be delivered in an environment free of infection. Masks should be worn by all those in attendance, and it is possible that some of us by reason of chronic nasal infection may not be able to undertake this special work.

A Final Suggestion.—We have learned much from the preparation of five-year reports on the results of examination, classification, and treatment of cancer of the uterus, particularly the cervix. By study of individual cases, methods of diagnosis and treatment, and as the result of comparison with the results of other observers, progress of a sound type has occurred. I would therefore suggest that a similar procedure be adopted in obstetrics: each hospital where deliveries take place should annually prepare a statement of the year's

Seventh.—The broad and round ligaments, which in their usual position admittedly have little or no supportive action, but which after vaginal hysterectomy, may be employed as a very real support both for the bladder and the vaginal vault.

Uterine prolapse and cystocele following childbirth are the results of stretching or tearing, or both, of the endopelvic fascial diaphragm, and the smooth muscle diaphragm, from their attachments to the uterus and bladder. In cystocele, the pubocervical segments of these diaphragms beneath the bladder may be split in the midline between cervix and pubis. The degree of herniation and prolapse depends upon the extent of the injury, the position and weight of the uterus, and varying degrees of intra-abdominal pressure, but it is facilitated by stretching or tearing of the muscular levator diaphragm which in turn enlarges the outlets below.

If in addition, the urogenital diaphragm, sphincteric muscle group, or the perineum be extensively lacerated, the uterus can prolapse to a still greater degree. Stretching or tearing of the rectovaginal prolongation of the endopelvic fascia completes the picture of prolapse with rectocele and possibly enterocele.

Advantages of Vaginal Hysterectomy in the Repair of Procidentia

Adequate reconstruction of the pelvic floor demands recognition and repair of all damaged structures; at the same time removal of irreparable, diseased, offensive or potentially troublesome tissues is indicated.

It is not enough, one would readily admit, to do an anterior colporrhaphy and a perineorrhaphy in a case of prolapsus. It is not enough to do as well an amputation of the cervix—even a high amputation. It may not be enough, either, to supplement these by bringing the lower portion of Mackenrodt's ligaments together in front of the amputated cervix, or even overlapping them with one or two sutures, especially if the uterus is large and the ligaments are poor. If high rectocele or enterocele or both are present, they must also be dealt with, and too often the repair of the upper posterior vagina is neglected.

Vaginal hysterectomy proffers ease in the complete management of all conditions related to prolapse. The sagging uterus is removed, giving free access to all the supporting structures possible: the uterosacral ligaments; the entire depth of the lateral cervical ligaments, with their lower smooth muscle and upper strong fascial components; the frequently thick and strong upper broad and round ligaments which may now be used as definite aids in supporting the new pelvic floor as well as the bladder. And finally, in the presence of enterocele or high rectocele, no other operative procedure can give equal exposure for their rectification.

One occasionally hears the opinion that the uterus is better left in, to act as a central supporting hub to which the stretched ligaments may be fastened. Yet do we worry about the vaginal vault when total abdominal hysterectomy is done? And is it not true that besides restoration of the pubocervical fascia, the main support usually given when vaginal hysterectomy is not performed, consists of one or two sutures, drawing the lower parametrial tissue together

VAGINAL REPAIR COMBINED WITH VAGINAL HYSTERECTOMY*†

J. E. HARRISON, M.D., C.M., VANCOUVER, B. C.

IT IS not intended herein to divulge some novel or simplified surgical procedure for vaginal repair with vaginal hysterectomy in varying degrees of prolapsus. Rather it is hoped to focus attention upon a sound operation which presents distinct advantages over certain other treatments of this affliction, and yet which is not commonly applied. It is felt that from experience gained through even a relatively small series of cases one might point out a few helpful ideas in a technique which, to be consistently successful, must be meticulous. Most of the literature on this subject to date lacks detail in description and passes over some of the important as well as some of the most difficult steps in the operation as if they did not exist.

Time will not here permit detailed discussion of anatomic considerations. The recent publication "The Pelvic Floor in Parturition" by Richard Power of Montreal, in *Surgery, Gynecology and Obstetrics*, September, 1946, treats this portion of the subject so well that one could do no better than to recommend its careful perusal. Suffice it to mention here the supporting pelvic structures which one must be familiar with, in order to reconstruct properly a broken-down pelvic floor after vaginal hysterectomy.

First.—The endopelvic fascial diaphragm or upper pelvic fascial floor, composed of (a) an anterior segment or pubocervical layer, representing the platform which supports the bladder; (b) the strong lateral segments or condensations, known as Mackenrodt's ligaments, or the lateral ligaments of the cervix; (c) the posterior segments or condensations known as the uterosacral ligaments. All three of these segments having attachment to pelvic bony structure, and to a definite fibrous fascial capsule, forming a collar about the supravaginal cervix. The rectovaginal septum is an extension of this capsule which descends caudally from its posterior margin, between vagina and rectum to terminate in the perineal body.

Second.—The smooth muscle diaphragm in the base of the broad ligament, lying between the endopelvic fascial diaphragm and the upper surface of the levator ani muscle. Smooth muscle bundles radiate from the uterus at the level of the internal os, imbedded in fibrous tissue below the upper pelvic fascial floor, and enter into the composition of the ligaments just mentioned.

Third.—The levator ani muscular diaphragm, whose anterior segment, the pubococcygeus muscle, forms the largest, strongest, and thickest part of the pelvic floor.

Fourth.—The urogenital diaphragm, composed of two leaves of fascia and containing mainly the sphincter urethrae, and deep transverse perineal muscles.

Fifth.—The sphincteric muscle group, whose action is only very slightly supportive.

Sixth.—The perineal body, whose importance in this connection is because each one of the diaphragms constituting the pelvic floor has an insertion into it.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

†For lack of space, it is not possible to include all of the illustrations submitted, but only those showing the essential features of the operation.

should not be considered, this argument does not face the light of fact. On the contrary, one is almost invariably impressed in cases of prolapsus, not only by the sense of physical well-being, but by the sense of mental relief which follows removal of the so-called offending organ.

Occasionally after repair with vaginal hysterectomy the patient is left with too short a vagina. Many of these cases are in the older age group to whom this complication is usually unimportant. It happens chiefly in the patients with complete sacropubic hernia, and in these instances one is likely to finish any type of operative procedure with a shortened vagina. In the younger group where the vagina is not already contracted, it is rare if certain principles in technique are adhered to.

Indications for Vaginal Hysterectomy With Vaginal Repair

Under this heading come first the group of women who are at or near the menopause, who have badly ulcerated tissues, severe bleeding, or irregular spotting, all of which arouse anxiety or fear of cancer. Even for the gynecologist and/or the pathologist, it is not always easy to exclude cancer by biopsy, either grossly or microscopically. In this age group also severe dysmenorrhea may logically be considered an excuse for hysterectomy when vaginal repair is done. The patient is relieved at once of a painful or bleeding organ.

In this and older age groups, where cervical cystic disease or hypertrophy indicates amputation of the cervix, is it not sound judgment to remove the whole organ, and thereby exclude the possibility of subsequent fundus cancer? We all apply this same principle in our modern concept of proper procedure in abdominal hysterectomy, and although admittedly cancer of the cervix is more common than cancer of the fundus, the latter is nonetheless a real hazard.

In women past the menopause it would seem too, apart from the advantages in repair of prolapse, that for the same reason, a logical prophylactic measure would be to remove an organ which is beyond physiologic usefulness.

In the younger age group other indications to be considered are cases of fibromyoma of the uterus, adenomyosis, intractable severe bleeding, and perhaps some instances where sterilization is deemed necessary.

A very real indication for vaginal hysterectomy with vaginal repair are those cases on whom previous inadequate repair has been done, with abdominal fixation of the uterus, and where there has been subsequently, recurrence of vaginal prolapse with the cervix remaining high. In these cases the uterus must first be released by laparotomy, followed by its extirpation through the vagina with proper restoration of the pelvic floor.

Contraindications

Removal of the uterus in the course of repair is definitely contraindicated in the younger women who have not yet completed their families. The other contraindications are fixation of the uterus or adnexa by old inflammatory disease or endometriosis, and intraligamentous or retroperitoneal growths or previous operations which might complicate procedure.

in front of the cervix? With vaginal hysterectomy all ligaments are shortened as indicated by the degree of prolapse, their stumps are firmly united on each side and then to their fellows on the opposite side. They are anchored securely to the subpubic fascia beneath the urethra, and finally the anterior vaginal wall is made fast to them. The ultimate effect, without the previous downward pressure of the sagging uterus, is that the contraction and shortening of the ligaments actually lift up the anterior vaginal wall and the vault.

Vaginal hysterectomy with repair is to be recommended in preference to high amputation of the cervix in any case, first, because with poorer exposure and subsequent reconstruction of the cervix there is more likelihood of damage to ureters, and second, because if the patient is in the childbearing age there is danger from future pregnancy.

There are also distinct advantages in this procedure over the method of vaginal repair plus abdominal hysterectomy in cases where removal of the uterus is indicated. There is less risk of injury to ureters and bladder, less risk of peritonitis, postoperative ileus or shock. In the fat or aged or debilitated patient it may be done easily and without shock under local anesthesia.

The advantages of vaginal hysterectomy over Watkin's interposition operation are self-evident. The latter does nothing which the former cannot accomplish, and of course leaves in an abnormal and awkward position a uterus which may become troublesome.

The operation for vaginal repair plus abdominal ventrofixation of the uterus needs mention only for condemnation as unsatisfactory and as an unnecessary hazard for the patient. Too frequently the surgeon who does this type of operation depends upon the fixation of the uterus to correct the prolapse, and so does an incomplete repair of the vagina. Many of these cases appear later with a recurrent cystocele or enterocele, and yet the cervix is held so high by ventrofixation that proper vaginal repair, alone, is impossible.

The patient who has had two or three repairs, and still has prolapse, is an ideal candidate for vaginal hysterectomy. Here one has access to an unused set of supporting structures, in place of old ones attenuated by repeated dissection and scarring.

Disadvantages

Vaginal repair with vaginal hysterectomy is definitely a more difficult and painstaking procedure than others, but if one familiarizes oneself with the technique it is not more dangerous, and in many instances is less dangerous. It is more time consuming excepting the case where repair and abdominal hysterectomy are done, but if the time consumption be not fatal to the patient, this should not be considered in comparison to the many other advantages. We all do the more difficult and longer operation of total abdominal hysterectomy rather than subtotal, because we believe it is a better operation for the patient.

One hears that it is bad physically and psychologically for a woman to lose her uterus, and with it her menses. Excepting the young woman who has not yet completed her family, and therefore of course, where the operation

The left index finger is carried through the cul-de-sac opening behind the right uterosacral ligament, to a point above it and close in to the uterus. Having decided how much tissue is to be ligated, depending upon the thickness and depth of the uterosacral and lateral cervical ligaments, a crushing clamplike heavy Oeschner forceps is applied for a moment to thin out and groove the tissue. This is removed and replaced by a ligature of No. 2 chromic catgut, carried through by a ligature carrier from the anterior surface of the parametrium, to the tip of the index finger close to the uterus in the cul-de-sac. A small but useful point in the tying of fairly large "bites" of parametrial tissue is that the assistant should relax his pull on the cervix as the knot is made. Otherwise tension on the tissues will prevent a securely fastened knot. The crushing of the tissue first also makes possible a more securely tied ligature, and the grooving insures against subsequent "slippage." The ligature is held long and the parametrium and uterosacral attachment is divided at least one-fourth of an inch distal to it. Provision of a generous stump distal to the ligature also prevents ligature "slippage."

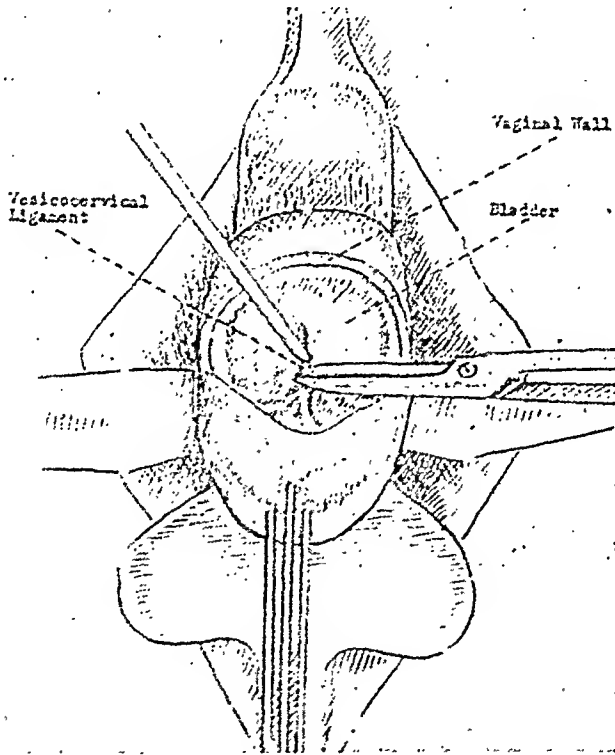


FIG. 1.—The vesicocervical ligament, extending to the cervix from the junction of the floor and posterior wall of the bladder, has been caught with toothed thumb forceps and lifted up to appear as a sagittal fold. This fold is placed on tension by traction on the floor of the bladder toward the symphysis, and is incised with scissors held at right angles to it, midway between bladder and cervix, to open the vesicocervical space.

Carrying the finger higher up the posterior surface of the parametrium, this crushing, ligation, and division of supporting structure is repeated once or twice, depending upon the depth of tissue forming the ligament of Mackenrodt. These ligatures are held long in one forceps. The uterine blood vessels are easily recognized and ligated close to the uterus. This ligature is cut short, so that it cannot be pulled off subsequently. The parametrial supports and vessels on the left side are now ligated and severed from the uterus in the same manner. With each step, the uterus pulls down more readily, exposure improves, and with the main blood supply interrupted, bleeding is negligible.

Technique

If the operation is performed under anesthesia other than local, blood loss may be greatly diminished by preliminary injection of one-half cubic centimeter of pituitrin into the lower parametrium on either side.

The anterior lip of the cervix is pulled well down with volsellum forceps, and the anterior vaginal wall incised transversely just above the point at which it becomes fixed to the cervix. If incision is made below this point, one may have difficulty in identifying the vesicocervical ligament, through which entrance is easily gained to the space between bladder and cervix. The incision is carried through mucosa and fascia, so that it will gape widely with upward retraction of the vaginal wall, and expose clearly the juncture of bladder and cervix. To further improve exposure one may dissect the anterior vaginal wall from the underlying bladder with curved blunt-pointed scissors, upwards for an inch or so, dividing the freed wall in the midline and retracting the mucosal edges. This will give full view of the vertical fibers of the vesicocervical ligament, which separates the vesicocervical from the already opened vesicovaginal space. The ligament is grasped with toothed thumb forceps, lifted up to appear as a sagittal fold (Fig. 1), and is incised with scissors held tangent to the surface of the bladder midway between bladder and cervix. This opens the vesicocervical space from below much more accurately than can be done with blunt gauze dissection. With traction downward on the cervix, first one index finger and then both are slipped up into the loose connective tissue beneath the bladder (Fig. 2) to separate the attachments between bladder and uterus completely. One not only reaches upward as high as possible, but separating the fingers widely, pushes laterally to free the base of the bladder and the ureters from the broad ligaments beneath.

The cervix is next pulled toward the symphysis, a posterior weighted speculum holding the vaginal tissues toward the sacrum. A transverse incision is made through mucosa and fascia of the posterior vaginal wall at the same level as that already made in the anterior wall. This incision may not overlie the tip of the pouch of Douglas, especially if the cervix be hypertrophied and elongated, but an incision made further down the posterior wall than this would shorten the vagina accordingly, and should be avoided. One may divide the wall vertically in the midline from this point downwards until the peritoneum is reached, and remembering the proximity of the rectum to vaginal wall, the opening into the peritoneal cavity should be made close to the uterus. The peritoneum of Douglas' pouch is incised transversely, and its lower margin made fast with a suture to the adjacent margin of the vaginal wall. A wide posterior speculum is then slipped into the pouch of Douglas, and, if omentum or bowel is seen, the head of the table is dropped to carry them up out of the operative field, or a taped sponge is placed within the cul-de-sac. If unusual difficulty is encountered in finding the peritoneum of the cul-de-sac, due perhaps to obliterative adhesions within, the uterovesical pouch of peritoneum is opened and a finger is carried down behind the uterus to push the cul-de-sac forward through the posterior wall incision into plain view.

The ends of the anterior and posterior vaginal incisions are joined by lateral incisions through mucosa only, and the upper leaf of the mucosa on either side is pushed with gauze well up to the level of the internal os. Superficial fibres of the lower parametrium are snipped and also pushed up, to carry a possible vagrant low-looping ureter out of harm's way.

A wide retractor is now placed beneath the bladder in the uterovesical space (uterovesical peritoneum still unopened), and, holding the bladder well forward, the cervix is pulled posteriorly and to the patient's left, thus drawing the right ureter well away from the uterus.

The entire border of the peritoneal opening into the pelvis is now exposed, and just external to it, lying on either side, are the stumps of the uterosacral, lateral cervical, and upper broad ligaments. These upper and lower ligament stumps with intervening endopelvic fascia are next sutured together on either side, so as to make two lateral massive ligamentous supports which will be united later to form the new pelvic floor.

Closure of the peritoneal cavity is effected with a purse-string suture of No. 1 plain catgut, placed just above the free edge of peritoneum inside the broad ligament stumps (Fig. 4). Care is exercised to avoid large blood vessels and ureters by taking shallow bites with the needle. In the presence of an enterocele, the purse-string suture crosses the cul-de-sac at a sufficiently high level to exclude all redundant peritoneum. This is then dissected out and excised. To facilitate the placing of the purse string, which can be difficult, it is safer to draw down the broad ligament stumps with forceps, rather than to pull them down by their ligatures. Inclusion of ovary, omentum, bowel, or the fimbriated tube end, must be avoided as the purse string is tightened.

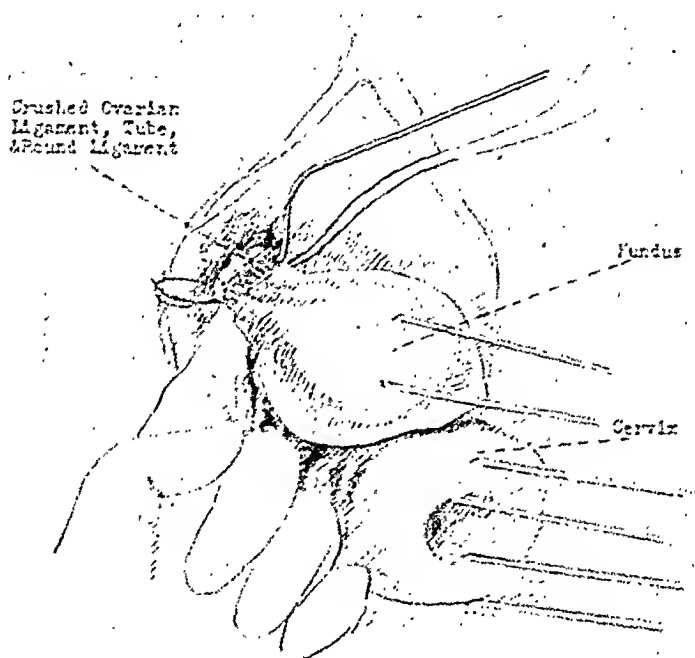


FIG. 3.—The fundus of the uterus has been drawn through the opening in the vesicouterine pouch of peritoneum. The right ovarian ligament, tube, and round ligament have been crushed, and a chrome catgut ligature is being placed to tie off these structures before cutting them away from the uterus. A stump a quarter of an inch long is left distal to the ligature. The remaining broad ligament below these structures is ligated and cut away from the uterus.

Repair of cystocele or urethrocele is now begun by dissection with curved blunt-pointed scissors to free the vaginal mucosa from the underlying fascia. The vaginal wall is divided in the midline to just below the urethra, and flaps raised laterally to expose the redundant bladder. On each side of the urethra, the dissection should be carried to the pubic arch to break down old traumatic adhesions which may interfere with sphincteric function. The strong sub-urethral fascia (cranial portion of the urogenital diaphragm) covering the neck of the bladder is plicated with two or three superimposed mattress type sutures of No. 0 chrome catgut. The importance of this minor procedure in every case cannot be overemphasized, for not uncommonly has the preparation of the anterior wall for repair, without this precaution, caused incontinence in

The uterovesical fold of peritoneum is easily identified and is incised transversely. Its upper edge is secured with one or two sutures held long to prevent its retraction upwards behind the bladder, and the retractor under the bladder is replaced by another inserted into the uterovesical pouch. The fundus uteri is grasped with a single toothed volsellum forceps and "tugged" out through this opening. In some instances this maneuver is facilitated by replacing the cervix in the upper posterior vagina. Depending upon the size of the uterus, it may be necessary to deliver the fundus with successively applied tenacula. In the case of the larger fibroid uterus this is supplemented by cutting out wide deep wedges of tissue held in the tenacula until the fundus

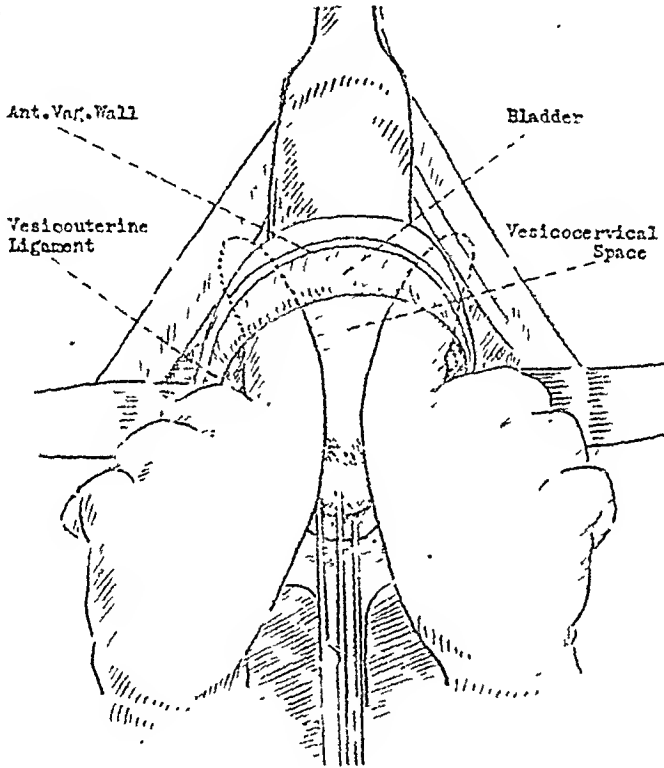


Fig. 2.—The vesicocervical space is entered with the index fingers, and as traction downward is made on the cervix, the bladder is freed from the uterus and broad ligaments, as high and as far laterally as possible. This is done to minimize the possibility of subsequent damage to ureters.

is small enough to deliver. At times one will encounter unforeseen adhesions involving bowel, omentum, or adnexa, but as the uterus is brought more fully into and through the opening, these may usually be dealt with simply. Particular difficulty may be overcome by bisection of the uterus, when the hand can be introduced into the pelvic cavity for further examination and exposure.

When the fundus is delivered (Fig. 3), the upper broad ligaments, including tube, ovarian and round ligaments, are first crushed with forceps as mentioned above, ligated with chromic catgut No. 2, and severed from the uterus, leaving a stump one-fourth of an inch distal to the ligature. The point chosen for ligation will depend upon the degree of prolapse, and the amount of shortening of the structures desired for rebuilding a firm pelvic floor. These ligatures are held long. The remaining portions of broad ligament are ligated and cut away to remove the uterus completely.

The anterior retractor is withdrawn from the uterovesical region of the peritoneal cavity, and replaced between peritoneum and bladder. The posterior retractor is withdrawn from the cul-de-sac and replaced by a short-bladed weighted speculum.

be extended downward toward the perineum. Usually, however, one incises the perineum transversely, and with blunt scissors dissects free the mucosa from the underlying rectovaginal fascia. In the higher, thinner central portion where the rectum is in closer apposition to the vagina, the mucosa is peeled off by gauze dissection. This should be carried up to the open vault of the vagina and the mucosal flaps raised laterally to expose the stronger lateral fascial regions, and in the lower vagina, the fascial covering of the levator ani muscles.

A crown suture (Fig. 6) is inserted at the vault, uniting the stronger lateral rectovaginal fascial areas and bases of the vaginal mucosal flaps to the uterosacral and lower broad ligament stumps above. The posterior wall fascia is then sutured with interrupted No. 0 chromic catgut (Fig. 7) uniting the fascia near the bases of the vaginal mucosal flaps and in the lower vagina, the sheaths of the levators ani.

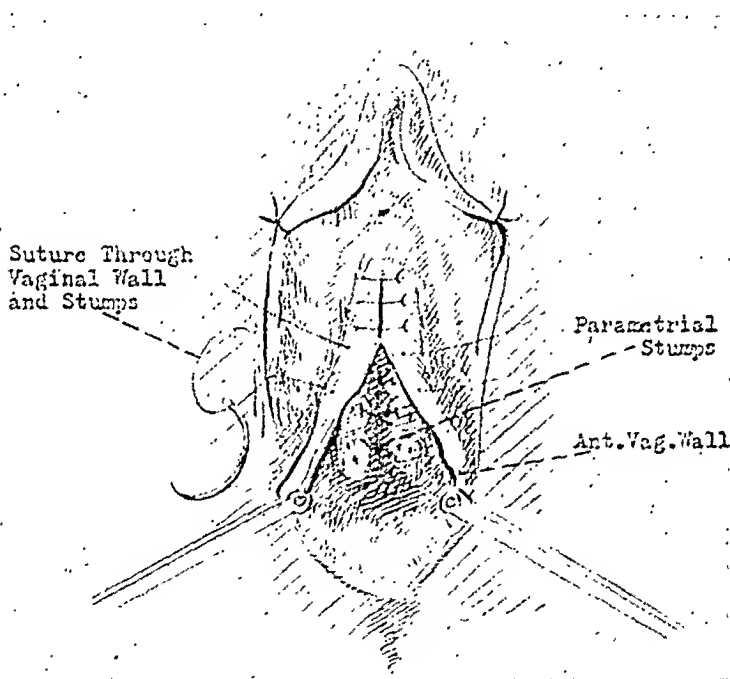


Fig. 5.—All upper and lower broad ligament stump ligatures on the left side have been tied to those on the right and cut short. Vaginal mucosa flaps have been trimmed and the margins are united with interrupted chromic catgut, several of these being passed deeply through the underlying broad ligament stumps. This not only firmly unites the ligamentous supports, but as they retract they will draw the anterior vaginal wall and vaginal vault upward, and increase the length of the vagina. The opening at the vaginal vault is closed excepting for insertion of a small gauze drain, unless high rectocele or enterocele must be dealt with. Then it is left open.

The mucosal flaps are trimmed and their margins united by a continuous stitch of No. 0 chromic catgut picking up small "bites" of the underlying fascia to close "dead space."

The lateral regions of the perineal incision are incised to permit withdrawal of the lower ends of the levator muscles, and these are united with interrupted catgut, the lower stitch picking up anterior fibers of the anal sphincter. The constrictor cunn muscle is restored by a single suture biting deeply into the labia majora. Transverse perineal muscles are united by a running suture of No. 0 chromic catgut which is continued subcuticularly to close the perineum.

a previously continent patient. In large cystoceles, the bulging bladder is reduced with a running suture uniting the strong lateral portions of pubo-cervical fascia.

The upper broad ligament stumps previously made fast to the parametrial and uterosacral stumps are now drawn out and forward with forceps to a position beneath the neck of the bladder. A mattress suture of No. 2 chromic catgut is passed through the subpubic ligament and fascia on the left, deeply through both upper broad ligament stumps to the right subpubic ligament and then back through the stumps to be tied at its point of entry. A second suture in support of this sling is passed from outside the base of the anterior vaginal wall flap on the left, through the subpubic ligament and stumps, and out through the right subpubic ligament and vaginal flap base to be tied later during closure of the anterior wall.

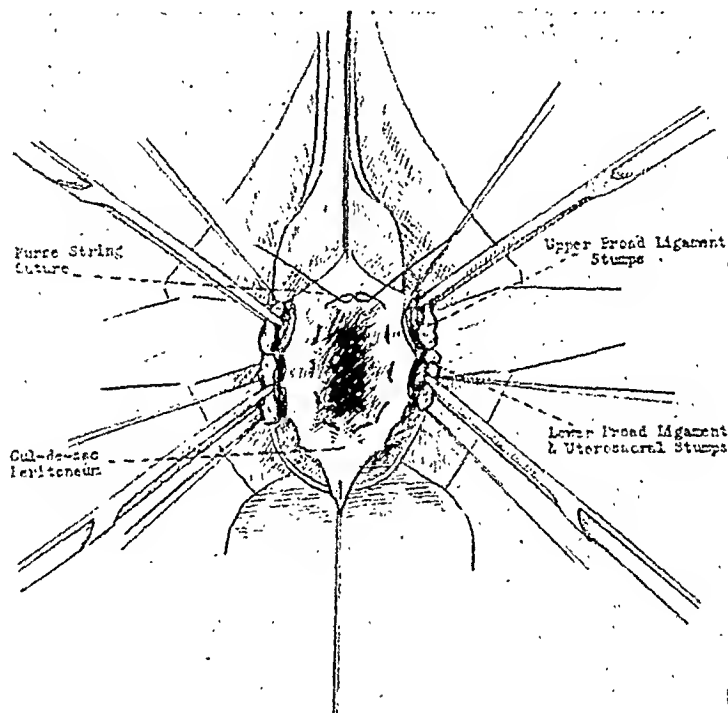


Fig. 4.—Upper and lower broad ligament stumps on each side are shown being drawn outwards and laterally by four forceps, to expose the entire peritoneal opening for insertion of the purse-string suture which will close it. The use of forceps makes it unnecessary to pull the stumps outward by their ligatures which might slip off. If enterocele be present, the purse string passes across the pouch of Douglas at a high level and excess peritoneum below is dissected free and excised.

Upper and lower broad ligament stump ligatures which have been held long are now tied to their fellows on the opposite side to unite the lateral halves of the new pelvic floor.

Excess vaginal flaps are trimmed, and the margins united with interrupted chromic catgut (Fig. 5). Three or four of these sutures are passed deeply through the underlying ligaments which later will contract and pull the vaginal wall up with them. A small gauze drain is left through the suture line near the vault to drain the stump area. It is removed on the fourth post-operative day.

If no enterocele or high rectocele exists, the vault may be closed and the operation completed by a low colporrhaphy and perineorrhaphy. In the presence of enterocele or high rectocele the vault is not yet closed. Incision through the mucosa may be begun where the cul-de-sac was previously entered and may

TABLE I. CASES, END RESULTS, AND COMPLICATIONS

CASES	NUMBER	REMARKS
Total	77	Average age—50.5 Oldest—85 Youngest—35
Prolapse		
3rd Degree	23	Average age—59.3
2nd Degree	15	Average age—51.4
1st Degree	39	Average age—44.4 including such other indications as abnormal bleeding, severe dysmenorrhea, diseased cervix, large cystocele, etc.
Previous operations	3	Previous vaginal repairs with abdominal fixation of the uterus, and cervix high in vagina, necessitating laparotomy first
Fibroid uterus	13	Five cases of 3 to 3½ months' pregnancy size. Eight cases of lesser size.
Malignancy	3	Ages (a) 46, (b) 64, (c) 69 years Cases (a) and (b) were adenocarcinoma of fundus. Both had postoperative x-radiation therapy. Both well and no recurrence at four and five years postoperative. Case (c) was an early squamous cell cancer of a protruding uterine polyp. No irradiation. Developed recurrence in vaginal vault in 1½ years and died four years after operation
<i>End Results</i>		
Mortality	0	
Recurrence		
Cystocele	0	Size of walnut above a low colporrhaphy. Patient apparently unaware because no complaints
Rectocele	1	
Enterocoele	0	At time of reading of paper one case was having nocturnal incontinence only. Since then she has cleared up entirely on estrin therapy
Incontinence	0	
<i>Complications</i>		
Hemorrhage	1	Occurred on the 18th postoperative day from slight slough of upper posterior vaginal wall
Cystitis		A common postoperative complication due to surgical trauma and frequent catheterization. Not more common than with other methods of repair. May be lessened greatly by strapping in a plain catheter, which is released when bladder fills (q 6 to 12 hours) and prophylactic administration of sulfadiazine, grs viiss q.i.d. for 5 days
Ureterovaginal fistula	0	
Vesicovaginal fistula	0	
Rectovaginal fistula	0	
Small vagina	8	Average age 68 years

Summary

1. The most important anatomical considerations are briefly outlined.
2. Advantages of vaginal hysterectomy in the repair of procidentia are discussed.
3. The disadvantages of the operation are considered.
4. A detailed technique of operation is described.

Conclusions

1. The literature on vaginal hysterectomy with vaginal repair to date, mainly lacks detailed description of operative technique.

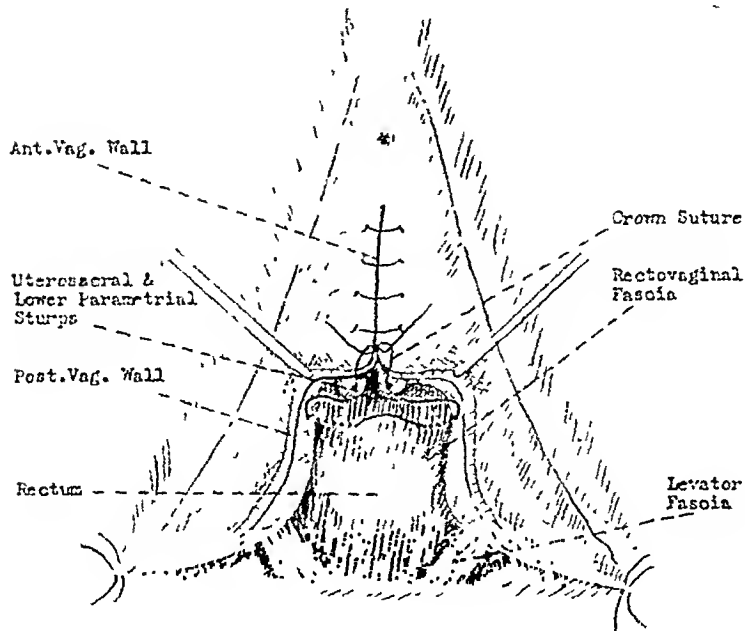


Fig. 6.—This figure shows exposure of the rectovaginal fascia up to the vault of the vagina, and the fascia covering the levator muscles in the lower vagina. In the vault are seen the posterior portions of the uterosacral and lower parametrial stumps. A crown suture of chromic No. 2 catgut has been placed to unite these stumps to the bases of the vaginal mucosa flaps, and the lateral portions of the rectovaginal fascia. This is an important step in the prevention of enterocele recurrence.

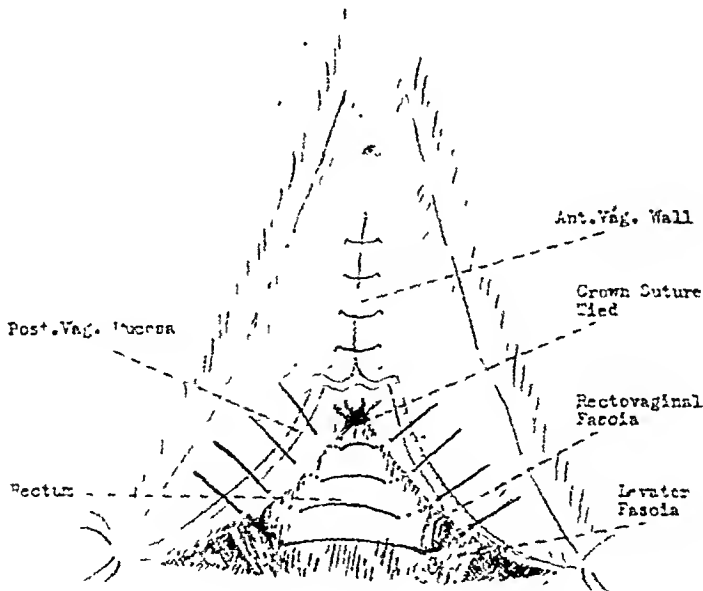


Fig. 7.—The vault of the vagina has been closed by tying the crown suture. A small gauze drain should be shown emerging from the anterior wall just above this point. The rectocele is reduced with interrupted No. 0 chromic catgut sutures, drawing together the bases of the vaginal mucosa flaps and the stronger lateral portions of the rectovaginal fascia. In the lower vagina these sutures include the anterior borders of the levator muscles and their fascial coverings.

STERILITY IN THE FEMALE*

KENNETH M. GRANT, B.Sc., M.D., C.M., HALIFAX, NOVA SCOTIA

THE problem of sterility has always assumed considerable importance in the practice of the gynecologist. In fact, there are few problems which test his training, patience, and breadth of knowledge more than that of sterility.¹ No less than 10 to 12 per cent of all marriages are barren. A number of gynecologic lesions may be factors in sterility, yet in recent years much light has been thrown on that large group of cases in which endocrine and physiological factors play an all-important role in its etiology.

The terms sterility and infertility are sometimes incorrectly designated as synonymous. According to Meaker² "sterility is the inability to initiate the reproductive process on the part of a couple who have desired and who have attempted to reproduce for a reasonable length of time, ordinarily at least a year." Some suggest three to five years, though less than 10 per cent of initial pregnancies occur after two years. "Infertility" is a term embracing any degree of conceptive capacity below the level of physiologic perfection, or the failure to produce a viable child.

From a clinical viewpoint, sterility in a mating is inability to reproduce, and the fault may be that of either the male or female or both, hence the fertility of a couple must be considered.³

Absolute sterility is a condition in which conception is clearly impossible. It is generally due to congenital malformation, such as absence or atrophy of the uterus or gonads, absence of vagina, or to complete occlusion of the Fallopian tubes or ductus deferentes, or when destructive disease has rendered one incapable of fertilization.

Relative sterility is one in which conception may occur, but various factors may make it difficult until existing precluding factors in either mate are corrected. Examples of such include endocrine and metabolic dyscrasias as well as local anatomic defects or lesions.

Acquired sterility is usually considered as the failure of conception after one or more children. It may be due to injuries, operations, new growths, metabolic disturbances, etc.

Selective sterility and fertility are terms used where an individual proves fruitful by one mate but barren by another.

Since the scope of this paper is primarily intended to cover the couple who present themselves seeking a reason for lack of conception, no attempt will be made to cover the subject in minute detail, but rather to outline a reasonably thorough and effective plan of investigation and treatment where indicated.

From the title of this paper one might infer that the female is altogether at fault. Such is certainly not intended, however, as the male partner must bear a considerable portion of fault in the study of childless marriages. Al-

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2. It is felt that this lack of detail may contribute to the fact that the operation is not performed more widely by gynecologists.
3. Removal of the uterus during the course of vaginal repair is indicated far more frequently than it is practiced.
4. The operation presents distinct advantages in selected cases over any other form of treatment of procidentia.
5. Gynecologists in general should be encouraged to perform this operation.

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Discussion

DR. B. P. WATSON, New York, N. Y.—I should like to congratulate Dr. Harrison on one of the best expositions of the anatomy of the essential supports of the pelvic organs and the techniques for their repair that I have ever heard.

I agree with him entirely in his indications for vaginal hysterectomy. After child-bearing is over the uterus has no physiological function, and it should be removed if in doing so a better and stronger support to the pelvic diaphragm can be given.

It is essential in any repair to make sure that the vault of the vagina is properly supported, otherwise it may prolapse later, no matter how good a lower pelvic floor repair has been done.

The only detail which I seem to pay a little more attention to than does the speaker is in isolating the supporting fascia of the lower rectum and uniting it in front of any rectocele which may be present.

DR. HARRISON (Closing).—Dr. Campbell mentioned the larger uterus. I would agree that in the presence of various types of pelvic pathology, it would be difficult to peritonealize raw areas. This does not necessarily apply to the fibroid uterus. Quite a few fibroid uteri up to three to three and one-half months' pregnancy size have been removed per vaginam without undue difficulty. This has not been done without some degree of relaxation of the vagina, or prolapse. I would agree, if any operation involved difficulty in closing the peritoneum cleanly. In two or three patients who had had previous Gilliam suspension operations, and whose round ligaments had stretched with prolapse, utilization of these ligaments and peritonealization was not a problem.

I did not say, Dr. Campbell, that I use a running suture in the anterior wall, because I never do. I did say that if the cystocele were of such a size that it required reduction and additional support, a running suture is used to plicate the fascia covering the bladder above the repaired sphincter. The vaginal mucosa is closed with interrupted sutures and some of these should extend deeply to include the underlying ligament stumps.

I have experienced no trouble with estrogen regarding increased friability of tissue. I do not see what would be gained by two or three days' treatment. This, in my opinion, could not improve the circulation and the tone of the tissues sufficiently. I have given small quantities orally over a period of three to four weeks before operation and have not run into the difficulty mentioned.

One should note particularly the history of acute general infections (scarlet fever), debilitating diseases, nephritis, venereal diseases, appendectomy (especially if patient had drainage), and pelvic operations. (2) A complete physical examination; routine blood and urine tests; evaluation of endocrinological stigmata. (3) A careful examination of the female generative tract, with special reference to the cervix. (4) Examination of the semen. (5) Hühner postcoital test. (6) Tubal patency tests. Hysterograms. (7) Investigation of the endocrine system.

Most, if not all, of the above investigation can be carried out in three office visits or less, depending on the findings. (To obtain the history of a couple, it is usually advisable to consult each one at separate times. In this way premarital incidents are more freely discussed and may be of value in the investigation.)

At her first visit the medical history should incorporate special reference to sexual activity and habits (coital, dietary, etc.), a careful menstrual history, for the menses can usually be considered a fair index of the reproductive development of the patient. Irregularities should be carefully noted and considered as possibly connected with ovarian dysfunction, whereas normal cyclic bleeding, while usually indicating normal function, may occur with anovulatory cycles. Her husband's health should be inquired into, as well as any other factors concerned with sterility, such as difficulties with the sexual act, or the actions of the female partner following intercourse. She is then given a complete physical examination, which should include routine blood tests and serology, urinalysis, and blood pressure. A clinical evaluation should be made of any endocrinologic stigmata from her skeletal configuration, her height, weight, distribution of hair and fat and secondary sex characteristics. Although all of the endocrine glands are more or less intimately related, in fertility it is becoming more apparent that the pituitary is essentially the gland of greatest importance, because of its direct action on the gonads, and indirectly on the thyroid, adrenals, and others.

After the medical examination, the gynecologic examination should follow, and include not only the pelvic but the functional examination as well.

Pelvic examination.—

Special points to be noted are:

1. *Infection in the lower genital tract, including the cervix:* The eradication of vaginal and cervical infections often yields the most gratifying results, and must at least be considered contributory factors in some cases. It may not be easy to explain why such infections as *Trichomonas vaginitis* and erosion of the cervix produce infertility in some and not in others, but their removal has certainly resulted in pregnancy in not a few of my own cases. This is especially true of erosion of the cervix, the cauterization of which ranks high as a therapeutic measure in sterility. (Caution should be exercised in too deep cauterization and cauterization very soon after the cessation of the menstrual flow to avoid secondary hemorrhage which may be very troublesome.)

though some estimate the male to share or accept full responsibility in more than one-half of the cases of childless union,⁴ in my own series the incidence was slightly less than 25 per cent. Percentages undoubtedly vary under different social and racial conditions.

In the investigation of sterility in the female, a balanced outlook must be maintained. Laboratory methods, though necessary, should not be depended upon entirely, but incorporated with the results of investigations of the reproductive system in particular and the clinical examination of the patient as a whole.

Parker⁵ states, "In order to evaluate the individual case properly the complete cooperation and examination of both partners are essential. The complexity of the problem, at times, and the necessity for repeated examinations must be impressed upon them."

Complete investigation into such a case and its proper treatment may be so complex and distributed over such a wide field as to involve the internist, the gynecologist, the urologist, the endocrinologist, the psychologist, as well as the roentgenologist. Such an inquiry has obvious and practical advantages, such as the elimination, for one thing, of much worthless and harmful treatment of a sort all too prevalent and, in particular, such disasters as operations done for sterility upon the wives of absolutely sterile men. Only if one partner is found to be incurably sterile is it permissible to dispense with the investigation of the other. Also by means of a complete study the most efficient treatment will be effected.⁶

It is obvious, of course, that pregnancy can occur only when the following conditions obtain: (1) Healthy sperm must be deposited at or within the cervical canal. (2) The sperm must be able to ascend without interference and at the proper time to fertilize a healthy ovum. (3) The ovum must implant itself on a suitably prepared endometrium.

Incidence.—Douglas⁸ states that 70 per cent of sterile couples show more than one causative factor. In a series of 48 unselected private patients, a single factor was noted in almost 60 per cent of them, and several factors were not commonly encountered.

Investigation.—Gardner⁹ states that many factors may contribute to the causation of infertility and that it is necessary to discover and correct as many of these as possible in order to achieve success. The examination should be thorough, can be done efficiently, and much discouragement avoided by adopting a simple but definite plan of investigation and completing it.

The day is fortunately passing, I believe, though repercussions of it are still noted, when a woman complaining of sterility is first advised to have a dilatation and curettage or to have a retroverted uterus corrected by operation, or because of an infantile uterus she is not likely to become pregnant, before a proper inquiry and investigation are carried out, preferably on both partners. Stein¹⁰ says, "the dilatation and curettage are often dispensable, the retroversion often of little consequence, and infantile uterus is usually an inaccurate diagnosis."

The diagnostic inquiry should include the following: (1) A complete medical history preferably of both partners, with special reference to sex history, coital habits, dietary habits, etc., should precede special sterility studies.

If a pelvic examination under anesthesia is indicated, as when findings are difficult to evaluate, the time of choice would be just before the onset of the menstrual flow, when an endometrial biopsy can be performed.

There is apparently some disagreement among gynecologists whether uterine fibroids play much part in causing sterility. I feel they are not particularly important unless of such profound size as to distort the cavity of the uterus or cause blockage to the Fallopian tubes. They are more likely to alter the course of a pregnancy rather than preventing its initiation.

Bilateral cystic ovaries, either as a result of hormonal imbalance or new growths certainly play a role in sterility, as pregnancy is a rarity in such cases.

4. *Examination of the semen:* Heckel¹¹ states that "the final diagnosis of the relative sterility or fertility of a man can be made only by the appraisal of the seminal fluid." If the semen conforms to the normal standards, further examination of the husband is probably not necessary; if not, a physical examination of the husband should be done with special reference to undescended testes, testicular atrophy, and metabolic or endocrine disturbances.

After several days of continence the specimen is preferably collected in a clean and dry glass container, following coitus interruptus, transferred immediately to a clean test tube, corked and placed in sufficiently close proximity to the body to maintain reasonable warmth, and brought to the office or laboratory within an hour. The collection by means of a condom, under similar conditions, in my own experience, does not seem as hazardous to the motility of the sperms as most authorities would have us believe, and I use this method frequently, as less handling is entailed and more constant temperature assured.

The important feature of the examination is the sperm count. Using a white blood counting pipette, diluting 1:20 with 5 per cent sodium bicarbonate solution, counting five blocks of sixteen squares and adding six zeros. An average normal specimen should contain approximately 100,000,000 spermatozoa per c.c., at least 80 to 85 per cent normally formed, and 75 to 90 per cent should exhibit active motility for some hours at room temperature.

The stained smear is also important, and less than 20 per cent should be abnormal.

It would seem wise, therefore, to refer to an interested urologist all husbands whose semen does not conform to those criteria just mentioned.

5. *Hühner postcoital test:* Though the next step usually undertaken is that of determining the patency, or nonpatency, of the Fallopian tubes, the Hühner test is now described as being more in keeping with the preceding paragraph. This is a simple and informative procedure, and requires only a few minutes. It should be performed at the time of ovulation, which is fourteen to fifteen days before the expected onset of the next menstrual period, when the cervical mucus is most receptive to sperms. It is wise to instruct the patient to empty her bladder and rectum before intercourse, and to report for examination within two to three hours following it, without taking a douche.

Samples are aspirated from the vaginal pool and from one, or preferably two levels in the cervical canal and placed on a slide, a cover glass placed over each and immediately examined under the microscope. Within the time allotted

The mere probing of the cervical canal by passing a uterine sound (a procedure I now do routinely at the first visit) has given such remarkable results, that in cases where no other gross abnormality exists in the pelvis I advise the patient to curtail further investigation a few months and await results. I feel some of the credit given to the insufflation of patent tubes rightly belongs to the passage of the cannula through the cervical canal.

It need hardly be emphasized that routine smears of the cervix and urethra to exclude gonococcal infection, and examination of Skene's and Bartholin glands should be made.

2. *Structural abnormalities:* In this group would fall those cases of arrested development of vulva, vagina, uterus, adnexa, the absence of one or more, and cases of unruptured or rigid hymen. Hypoplasia of the uterus can usually be suspected when the uterus is about the size of a small walnut, usually anteflexed but may be difficult to outline by palpation (if patient is fat) and when a long, conical cervix with pinhole external os is found. Though hypoplasia of the uterus does not invariably signify sterility, it is a rather common finding in many cases.

3. *Malpositions of the uterus and adnexa:* Retrodisplacement of the uterus has certainly been overemphasized, in the past, as a cause of sterility. However, when associated with a cervix which points toward the anterior vaginal wall, or behind the symphysis and away from the seminal pool, it assumes more importance as a factor. It is well known that many women with such findings readily conceive, and it is no longer common practice to radically correct such displacements. When such a uterus is mobile, it is much less likely to be a cause of infertility than one which is fixed by adhesions resulting from inflammatory disease or endometriosis. The use of a Hodge pessary in such cases, either with or without manual replacement of the uterus, is often successful as a therapeutic measure.

4. *Pelvic inflammatory disease:* Since this is one of the commonest causes of sterility, the adnexa must be completely palpated. It is manifested by the usual signs of tender tuboovarian masses, or indefinite thickening of the bases of the broad ligaments, partial or complete fixation of the uterus, and tenderness on movement of the cervix.

Endometriosis is probably often overlooked as a cause of sterility. I believe it is a rather frequent cause. I can recall several cases in which, on investigation, no known cause could be found for the sterility of the couple, but examination and operation sometime later revealed the presence of a well-established endometriosis. The explanation in early cases is difficult, as the Fallopian tubes are patent, ovulation is rhythmic, yet pregnancy is a rarity. The condition should be suspected when the patient complains of increasing dysmenorrhea which has been acquired during adult life, when the uterus is retroflexed and fixed, when the ovaries are enlarged, tender, and fixed, and when pain is referred to the rectum at the time of ovulation as well as at menstruation.

In my own practice, in most, though not all cases, choosing the proper time of the cycle, the patient is sent into the hospital for about twenty hours. On the morning following admission a basal metabolic rate is taken. Following this a hypodermic containing $\frac{1}{6}$ grain morphine and $\frac{1}{150}$ to $\frac{1}{200}$ grain scopolamine is given as a sedative and antispasmodic, and an hour later the tubal insufflation and lipiodol injection are carried out. (Methyltestosterone, given orally, in doses of 50 to 100 mg., serves as an excellent antispasmodic, especially when insufflations are carried out in office practice.) It is rarely necessary to use more than 6 or 7 c.c. of oil injected slowly. It is preferable, though not necessary, to watch the instillation through a screen, following which an x-ray is taken. A nonopaque speculum is desirable. Within six to seven hours another plate is taken to determine whether the lipiodol has passed into the peritoneal cavity. If not, the patient is instructed to return in forty-eight hours and another plate taken.

In most cases, where tubes are patent, little or no residue of oil is noted; where the tubes are blocked, it is still plainly visible within them.

The contraindications to the use of tubal insufflation and hystero-graphy are well known and include recent acute or subacute pelvic inflammatory disease, purulent cervical discharge with endocervicitis, infected urethral or Bartholin glands, menstruation or abnormal bleeding, following dilatation and curettage, cardiovascular and pulmonary disease, suspected pregnancy, and severe nervous disorders.

7. *Investigation of the endocrine system:* Gardner says,¹² "Healthy women of childbearing age, who menstruate normally and with some degree of regularity, probably also ovulate fairly regularly. However, individuals without gross genital pathologic changes, who either menstruate infrequently, flow irregularly and scantily, or bleed continuously, probably do not ovulate, such menstrual disorders usually resulting from disturbed function by the glands of internal secretion."

If the investigation so far reveals no obvious cause of sterility, the question of determining whether ovulation is occurring becomes important. Ovulation is difficult to prove. Only presumptive evidence of it may be obtained by endometrial biopsy, taken a few days before the onset of menstruation, or preferably shortly after its onset, to avoid the risk of interrupting an early pregnancy. Ovulation is assumed when the endometrium shows the secretory phase of corpus luteum stimulation. The procedure, however, occasionally is difficult to do, causes not a little pain in nulliparous women especially, and really gives information only for the one cycle reviewed. Recently I have used endometrial biopsy less, and basal body temperature curves more, and have been impressed by its advantages and usefulness. A pronounced biphasic curve is regarded as evidence that ovulation has occurred. At least two cycles must be taken.

Vaginal smears, and determination of the pregnandiol complex between the twentieth and twenty-fourth day are less reliable measures.

The number of cases of hypothyroidism seen in my own practice far exceeds that of any other endocrine problem. Even mild degrees of it are often asso-

above, if numerous actively motile sperms are seen in both samples, or five to fifteen active sperms present in the mucus from the cervical canal, one can then assume that intercourse has been properly consummated, that sperms are capable of ascending the cervical canal, and that endocervical secretions are receptive to them. Under such conditions one need not feel concerned about the position of the cervix, the length of the vagina, minor abnormalities of the male, such as epispadias, hypospadias, or premature ejaculation. If dead spermatozoa are found in the samples taken from the cervical canal, and active ones found in the vaginal pool, one can properly assume that some hostility exists between the sperms and the endocervical secretions. In such cases, eradication of the endocervicitis undoubtedly present will often result in curing many cases of sterility. I have found such a procedure pays dividends in very many instances. A word of caution is hereby interjected, however, against too extensive cauterization, such as conization, etc., owing to the extensive scar tissue formation which invariably follows such procedures.

6. *Tubal patency and hysterosalpingography*: Tubal insufflation, originally described by Rubin, has probably been the greatest single advance in the diagnosis and treatment of sterility in the female. I have used both carbon dioxide and filtered air, and must frankly state that I have found no difference in the use of either, the patient's reaction depending entirely on the amount insufflated and not on the agent used. I have found the Jarcho Pressometer eminently satisfactory for tubal insufflation.

It need hardly be emphasized that the test should be done within four or five days after the cessation of menstruation. Also that, under normal conditions, the gas passes through the oviducts at a pressure between 60 and 80 mm. of mercury. The rate of increase in pressure should be gradual to avoid spasm of the tubal musculature. The diagnosis of blocked oviducts should not be made definitely until insufflation has failed on three or four occasions, at the same or different sittings. It is probably unwise to carry the pressure beyond 200 mm., though I have seen no ill effects from exceeding this figure on a number of occasions.

Though most authors on the subject insist that the injection of radiopaque substances should be reserved for those cases of apparently stenosed tubes, for purposes of localization, I am quite sure that the use of such substances has a therapeutic value in some cases. Any ill effects from the use of lipiodol or similar oily preparations I have yet to encounter, and within recent years their use has been employed almost routinely in my own practice. The number of cases in whom tubal insufflation failed to bring about the desired results, yet became pregnant following shortly upon the injection of lipiodol, has been rather convincing of its value therapeutically. Also, the information obtained with respect to the location of the block, and the likelihood of success or failure of plastic operations on the tubes supports, to some extent at least, the value of the procedure. The use of supposedly less irritating substances such as Visco-Rayopaque of "Roche" has been advocated by various investigators, but I have had no experience with such to date.

Summary and Conclusions

The factors most commonly encountered in my own series of cases were more or less in order of frequency: cervical erosions and infections, mild degrees of cervical stenosis, hypothyroidism, tubal occlusion, and impaired quality of spermatozoa.

First office visit: A complete medical and gynecologic history is taken, followed by a complete physical examination with special reference to the pelvis. The cervical canal is probed.

A notation of the husband's health, age, habits, etc., are made. Blood serology on both should be done.

Instruction is given her how to take vaginal or rectal temperature. A chart recording this temperature, the menstrual cycle, and dates of coitus is explained and given to her to keep her own record for at least two cycles.

The husband's sperm analysis should be done before the next visit.

Treatment of vaginal discharges of known etiology is advised.

Second visit: If the above records and laboratory reports are satisfactory, a basal metabolic test, tubal insufflation, and, where indicated, uterotubograms are done. If the tubes are patent, she is instructed about the Hühner test.

Third visit: Examination is made of the semen from the vaginal pool and the cervix within one of two hours of coitus, at the expected time of ovulation.

Erosion of the cervix, endocervicitis, etc., are treated when indicated.

The completeness of one's investigation in each case will naturally vary somewhat with the findings. Where absolute sterility is found, further investigation is discontinued.

Our results in overcoming sterility will improve when we are prepared to investigate the infertility of both husband and wife, and not the wife alone. The cooperation of both is necessary.

The survey necessary for the complete investigation of both male and female partners has been presented. Where any abnormality in the male exists, he should be referred to a competent urologist or internist for further study.

The future program may necessitate repetition of doubtful tests.

Six months should be sufficient time to investigate an average case. When all diagnostic data have been correlated, the cause or causes for the sterile mating should be explained to the patients and the prognosis outlined on the basis of established methods of correction and treatment. Where specific treatment is being carried out, a longer time than this may be necessary to justify it. Patients quickly lose interest in their study if they are advised to return in six months or a year, following each bit of investigation carried out.

Physicians, in general, should heed the solicitations of the sterile couple, and, if not interested, should refer them to someone who is. Such patients are usually sincere in their quest, almost always cooperative, extremely grateful when success is achieved, and most deserving of careful investigation and patient study.

ciated with sterility. It is routine procedure with me, in all cases being investigated, to have basal metabolic determinations made, and where variations from the normal spermanalysis exist, to have the husband done also. It is my own feeling that any apparently healthy individual in the minus bracket properly belongs in this hypothyroid group, and that a rate as low as (-7) to (-10) , which we have been taught to consider within normal limits, is not so justified. Hypothyroid patients, even of mild degree, respond remarkably well to replacement therapy, and a few dollars' worth of thyroid will often pay dividends far in excess of many times this amount spent for more elaborate forms of therapy and investigation.

Some authorities mention the desirability of blood cholesterol determination, sugar tolerance tests, x-ray of the sella tureica, etc., but I feel they are not often indicated, and rarely offer much help.

Is there a psychologic factor in some cases? We all know of women infertile for years with no obvious reason quickly becoming pregnant following the adoption of a child. I can offer no scientific explanation.

Although it was not intended to discuss treatment in this paper, one should not merely mention endocrine investigation and leave it entirely at that. I am convinced that an appalling amount of time and energy expended in the past ten years or more in the indiscriminate use of sex hormone therapy in cases of sterility sometimes is unwarranted with harmful results.

Endocrine treatment of infertility in the female may be classified as follows: (1) treatment directed at correcting disturbances of endocrine glands which indirectly affect the reproductive processes; (2) treatment directed at correcting disturbances intrinsic in the ovary or uterus.

Siegler¹³ states that "in specific treatment the first factor to be considered is whether or not follicle maturation, ovulation, and its sequelae are properly taking place, and therapy should be individualized and cautiously and judiciously applied." He likewise states the necessity of determining which gland or glands are at fault, following which to administer the proper hormone in potent form, in adequate dosage, and over a sufficiently long time. One must remember, however, that excessive therapy eventually results in atrophy of the tissue which produces the hormone administered.

For my own part, except in cases of true genital hypoplasia, and the occasional case of irregular menstrual flow, which thyroid does not correct, female sex hormone is rarely used. In cases, however, where biopsy indicates lack of proper endometrial development, or where pregnandiol assays indicate lowered excretion (i.e., less than 35 mg. in the normal ten to twelve days), large doses of corpus luteum hormone should be tried. Henry¹⁴ apparently found it helpful in selected types of his so-called functionally sterile group. Hamblen¹⁵ covers this aspect of the subject in a masterly way in a recent publication.

Further details of treatment such as plastic operations on blocked tubes in selected cases, or operations on the male to correct aspermia or artificial insemination do not fall within the limits of this presentation.

AN IMPROVED OPERATIVE TECHNIQUE FOR SALPINGOSTOMY*

H. W. JOHNSTON, M.D., TORONTO, ONTARIO

(From the Department of Obstetrics and Gynecology, the University of Toronto, and the Gynaecological Wards of the Toronto General Hospital)

THE operation of salpingostomy whenever tubal occlusion exists is justifiable only when the patient insists on having a child. It is taken for granted that the husband is healthy and fertile. It is also taken for granted that at least two or three previous insufflations have been unsuccessful.

Obstruction in the Fallopian tubes may be present anywhere throughout the lumen. When it occurs at the uterine end, intrauterine tubal implantation is necessary to restore patency. I believe it is the feeling of most gynecologists that this is rarely a justifiable procedure. It does not appear to be surgically or anatomically sound. Salpingostomy, on the other hand, offers possibilities.

Previous to September, 1943, other methods had been attempted by me with no resulting pregnancies. The present technique was suggested when, in the first patient to be reported, a radical operation was about to be begun a few minutes after an unsuccessful insufflation. As the tubes were being handled preparatory to their removal, the striking distention and crepitus suggested a salpingostomy, even if in view of previous experience this operation seemed a forlorn hope.

Since 1943 I have performed salpingostomy three times by this method and, although it seems fantastic, in each case pregnancy followed within a year.

The Operation

The anesthetized patient is placed in the lithotomy position, and one more insufflation is attempted to determine the patency of the tubes. Air is forced into the uterine cavity, and maintained at a pressure of 225 mm. of mercury for two minutes. The intrauterine instrument, if this final test fails, is withdrawn, the patient changed to the Trendelenburg position, and the abdomen opened. Occasionally it is found that the diseased tubes are so irreparably ruined by the previous pathologic process that nothing in the way of a reconstructive operation is possible. However, more often, on palpating the tubes, crepitus will be obtained in one or both, proximal to the "block" which obstructed the distal flow of the air when insufflation was attempted a few minutes before. Even when the tubes are enormously distended as they are in hydrosalpinx, the crepitation is very distinctly palpable to the point of occlusion. At any rate, the practical point is this—that if the tube is incised along its free border at the point of maximum crepitation, a new ostium can be established. When this is performed, a mixture of air and "tubal content" debris gushes forth. As in

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Discussion

DR. MARION HILLIARD, Toronto.—I agree entirely with Dr. Grant's presentation of his investigation, organizing it into three major visits of the patient, one of them being in the hospital. It is difficult to rule out a great many patients who just want to see if they are normal. I have found that 33½ per cent of the patients do not return when they find that a complete investigation is necessary both for themselves and their husbands. In my practice I send all the husbands to a urologist who is interested in this type of investigation and treatment.

I have found the use of Hodge pessaries of great value in cases of retroversion of the uterus, and would like to mention that these pessaries are good in cases of acute antelexion when the cervix is well up in front.

In a discussion of the relative diagnostic values of the Rubin test versus hysterosalpingograms, I have found it possible to put oil through the tube when it was impossible to be sure that air had gone through. Therefore, I would feel that a hysterosalpingogram would be necessary before an absolute diagnosis of sterility could be made. On the other hand, wherever there is any other gynecologic complaint such as intermenstrual discharge, dysmenorrhea, or profuse periods, a dilatation and curettage with the insufflation of tubes will have good therapeutic effect. I use hysterosalpingograms almost entirely and find them very successful. In a series of eighty-four cases, sixteen showed definite abnormalities without any previous histories of any gynecologic complaint or operative interference.

As to the use of thyroid, I agree with Dr. Grant entirely. I put my patients on one grain of thyroid daily, if the basal metabolism rate is not over plus six or seven. There has been some discussion as to whether this may not depress the normal thyroid function, if given over a period of time.

DR. GERIN-LAJOIE, Montreal.—I would like to stress that in our clinic we seldom do an insufflation test. We always use uterosalpingography with lipiodol with better results. We use it not only for sterility but for other diseases where it might be beneficial for the diagnosis. I would like to suggest the removal of the speculum before taking uterosalpingographs as advisable, for there might be findings which would be obscured.

probes, bristles, etc., into the uterine cavity. These procedures, involving as they do needless intratubal trauma are to be condemned. The gush of air when the scalpel opens the lumen is ample proof that the tube is patent, as far as the site selected for salpingostomy (See Fig. 1, A, B, and C).

Case Reports

CASE 1.—*Mrs. W.*, aged 28 years, was seen on Sept. 4, 1943. At 19 years of age she had married, and gave a history of pelvic inflammation following the mating. During the past four years, numerous attempts at insufflation were negative, and she had been told that her tubes were "blocked." On Sept. 17, 1943, a final testing was carried out. The pressure was raised to 225 mm. and kept constant for two minutes. The tubes were found to be closed. The abdomen was opened. The right tube showed the characteristic ravages of pelvic inflammation, and was in the quiescent state of hydrosalpinx. It was impossible to find any semblance of a natural ostium. A new one was fashioned over a suitable spot where the adhesions were least dense, and where crepitation was most easily elicited.

The left tube appeared edematous, and air had traveled along its lumen to its middle third. The outer third was bound down tightly to the sigmoid colon. A salpingostomy was done on this tube by slitting it along its free border at the spot of maximum crepitation. The abdomen was closed. The convalescence was uneventful. Ten months after the operation I received a letter from her physician stating that she had unfortunately miscarried in the midtrimester of a pregnancy.

CASE 2.—*Mrs. G.*, aged 28 years, was seen on June 12, 1944. This patient had been married for four years. A history of painful menorrhagia antedated her marriage. The pelvic findings were as follows. A retroverted, large, fixed uterus, with small bilateral masses. The cervix was clean. A tentative diagnosis of endometriosis was made. Previous tubal insufflations had been pronounced negative. Under anesthesia, a final testing was done. The tubes were closed. On opening the abdomen the diagnosis of endometriosis was confirmed. The right tube was occluded throughout the whole lumen, at least, there was no proof of air having passed as no crepitation was obtained.

The left tube and ovary were "dug out" of the pouch of Douglas. The tube was engorged with air as far as its distal third, and the fimbriated end was densely adherent to the ovary. A new ostium was fashioned over the free border of this tube at the point of maximum crepitation. The uterus was then suspended and the appendix removed. The convalescence was uneventful. The following year she conceived, and unfortunately miscarried. On Oct. 5, 1946, Dr. Adamson of Hamilton delivered her of a living female child.

CASE 3.—*Mrs. M.*, aged 25 years, was seen on Sept. 3, 1944. This patient had been married for five years. Previously she had been operated upon by a general surgeon for pelvic inflammation, and the appendix, the right ovary, and part of the right tube removed. The menses were regular and painless. On Oct. 21, 1944, a routine insufflation of the tubes was done, and it was found that the air at a steady pressure of 225 mm. of mercury failed to pass into the peritoneal cavity. The abdomen was then opened. The remaining part of the right tube was very distended, and "crackled" on palpation. It was about three-fourths inch long, and clothed with dense adhesions. After freeing the minimum of adhesions necessary to make the plastic change feasible, a curved half-moon incision was made over the free border and this was deepened until air and tubal debris oozed forth. A new orifice was fashioned using interrupted sutures of fine chromic surgical gut on an atraumatic needle.

these patients the insufflated tubal wall is thin and avascular usually, the bleeding is slight. This absence of troublesome bleeding is invaluable. For one of the dangers heretofore in salpingostomy was the formation of a hematoma during the fashioning of the new ostium. This, together with the adhesions which usually followed in its wake, invalidated the future success of the operation.

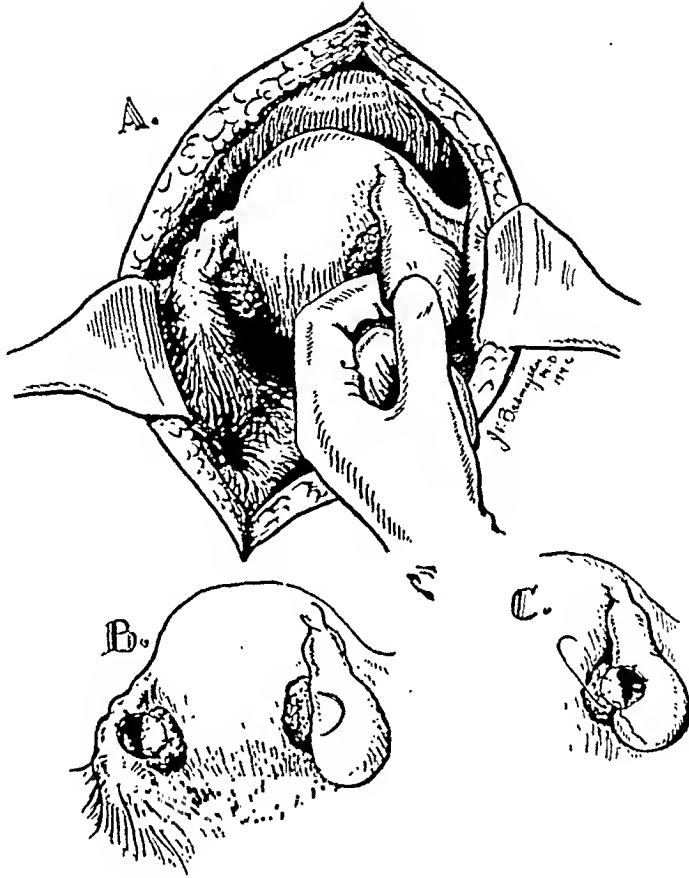


Fig. 1.—A, Exploring the abdomen and examining the Fallopian tubes. The tubes are closed. The patient has suffered from pelvic inflammation. The left hand of the surgeon is palpating the right tube. Over the area of maximum crepitation a new ostium will be fashioned.

B, Salpingostomy of the left tube. A curved incision (half-moon) opens the tube. This "trap-door" type of flap leaves a gaping wound, and there is very little chance of the ostium closing. The blood supply to the flap is preserved so that sloughing will not occur. By suturing it down to the ovarian hilum (which is practically avascular) every opportunity is given the ovum to tumble into the gaping mouth of the artificial ostium. The curved line on the right tube delineates the site of the incision.

C, Salpingostomy of the right tube. The flap is being sutured to the hilum of the ovary with fine chromic surgical gut on a small atraumatic needle.

The fashioning of the ostium may be left to the ingenuity of the surgeon. Fine silk or fine surgical gut on an atraumatic needle is advised. Any unnecessary separation of adhesions is to be avoided. Adhesions tend to reform. If it is possible to establish the artificial opening near the ovary, this should be done, but it should be remembered that the adnexa resent rough handling, and show their resentment in the form of troublesome oozing. As mentioned above, this may defeat the purpose of the operation. Nor is it necessary in this procedure to test the patency of the tubes from above by attempting to pass air, fluids.

A STUDY OF BREECH DELIVERY*

ALBERT E. TRITES, M.D., VANCOUVER, B. C.

(From The Vancouver General Hospital)

THE serious infant mortality associated with breech presentation is emphasized in all standard texts of obstetrics, the total uncorrected fetal death rate being placed at about 20 per cent. Stander states that approximately one-third of this loss is directly due to the presentation itself, while Holmes and Evans give the mortality for the child as 10 per cent. As suggested by Tompkins and others, it seems likely that the fetal risk has been exaggerated in the minds of obstetricians by the failure to distinguish between the infantile death rate associated with breech presentation and the mortality of breech delivery per se. The fact that the presentation is frequently associated with prematurity, placenta previa and fetal abnormalities must be borne in mind; all conditions carrying an inherent serious risk to the child.

Furthermore, statistics on breech delivery as published from large clinics are undoubtedly influenced by the fact that a considerable percentage of deliveries by interns in training is included.

Recent studies to determine the intrinsic risk of breech delivery present a more cheerful view of the picture. Hansen has collected a series of 112 consecutive cases from private practice with a corrected fetal mortality rate of 0.8 per cent. External version was not practiced, and the conduct of labor and delivery was most conservative. Tompkins has presented a series of 211 breech cases delivered by a group of 17 obstetricians in Philadelphia, all diplomates of the American Board of Obstetrics and Gynecology, with a corrected mortality rate of only 2.7 per cent. Perhaps the most striking results are those of Greig, who reports sixty personally delivered cases of breech presentation in primigravidas with but one stillbirth and no neonatal deaths. His method of delivery is extremely conservative, spontaneous birth with a minimum of manual assistance being the rule. Local (pudendal block) anesthesia was used, his recent cases having received no general anesthetic even for delivery of the head. Greig believes that fully 90 per cent of breech deliveries in primiparas can be spontaneous.

While admittedly these excellent results are reported by skilled obstetricians, it should be noted that in the conservative management, as recommended by Hansen and Greig, success depends more upon method than on manual dexterity, and that a similar technique therefore may be followed with considerable assurance, even by the neophyte in obstetrics.

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The left tube was now examined and found to be a typical hydrosalpinx with a closed fimbriated end. It had become enormously distended with air as a result of the attempted insufflation. The closed tube was separated from the outer pole of the ovary, and salpingostomy was performed simply by removing the distal part by circular amputation. On Dec. 20, 1945 (thirteen months after the operation), I delivered this woman of a living male child weighing 8 pounds 3 ounces.

Summary

Salpingostomy is justifiable in certain cases. It is admitted that the operation has a limited field of usefulness. A technique is described in which preparatory to laparotomy, air is forced into the uterus at a high pressure, and salpingostomy is then performed on the tube over the area of maximum erepitation.

Only three cases are reported, but the successful results seem to indicate the value of the method.

Discussion

DR. VAN WYCK, Toronto, Canada.—A review of the subject of plastic operations on the tube for the cure of sterility has not given a very favorable picture. The reason is threefold. The relatively few live babies achieved by these methods; the undue proportion of ectopic gestations resulting; and finally the complications which may from time to time follow any laparotomy.

Dr. Johnston has described a modification of technique in which he has utilized tubal insufflation: (1) To determine the point of obstruction. (2) To select the best operative site for fashioning a tubal ostium. The maintenance of the distention of the tube when the abdomen is opened, renders the operative site more avascular and the operation more practicable.

One cannot, in such a small series, draw many conclusions. One cannot, also, neglect the fortuitous. However, I should like to suggest one procedure which might be added to his method. The preliminary lipiodol salpingography might still further eliminate those cases where plastic operation might give no reasonable hope of success.

TABLE II. FETAL RESULTS IN BREECH DELIVERY. VANCOUVER GENERAL HOSPITAL GROUP
(JAN. 1, 1945, TO JULY 1, 1946)

NUMBER	STILLBIRTHS	NEONATAL DEATHS	FETAL MORTALITY
145	7	1	5.5%
	<i>Personal Group (1935 Onward)</i>		
55	1	1 (Congenital heart)	3.6%
		Corrected	1.8%
(Premature babies of less than 2,500 Gm., twins, and gross monstrosities excluded)			

There was no maternal mortality in the entire series.

The Management of the Patient

Granting the conclusion that fetal mortality is largely dependent upon the success or failure to achieve a spontaneous or nearly spontaneous delivery of the breech, the conduct of labor is directed to this end throughout. The procedure as described is chiefly applicable to delivery in primiparas, and is modified as necessary in multiparas.

To avoid unnecessary worry, the expectant mother with a breech presentation need not be informed of the fact before labor commences. If she is aware of it, the importance of the condition is not emphasized. However, when labor is established, it is well to acquaint her of the situation, and to enlist her aid for the delivery to come. One explains that since her active cooperation in the birth will be required, she will not receive deep analgesia or amnesia. To this end such drugs as paraldehyde, scopolamine, and the barbiturates in high dosage, which tend to cloud the sensorium and produce restlessness, are contraindicated. However, since uterine inertia is not uncommon, the patient is protected against exhaustion and dehydration by adequate sedation and fluid administration.

TABLE III. DETAILS OF PERSONAL SERIES

A. Number of Cases		60
	Primiparas	42
	Multiparas	18
	Average age of Primiparas	27
B. Type of Delivery		
	1. Spontaneous with manual aid	43
	2. Extraction	12
	3. Cesarean section	5
	4. Forceps to aftercoming head	18

When the cervix is believed to be fully dilated, the patient is prepared as for delivery, and a vaginal examination made to rule out the possibility of a prolapsed cord and to satisfy oneself that there is no remaining rim of the cervix. Not infrequently, and especially in footling presentations, the leading part may be visible at the vulva before cervical dilatation is complete. Premature expulsive efforts in such instances may result in the cervical rim offering obstruction to the aftercoming head. Sufficient time should be allowed to ensure that the cervix is not only completely dilated, but also "paralysed," as someone has aptly expressed it.

When we consider the effect of a more radical policy of delivery, namely elective breech extraction upon complete dilatation of the cervix, the fetal results are not comparable. Even in expert hands, the procedure is associated with a reported mortality for the child of from 6 to 10 per cent, although Goethals did succeed in achieving a mortality rate of 2.3 per cent in one series. Obviously, should the practice of elective extraction become widely adopted, the loss would be much greater. In an analysis of over 3,000 breech deliveries in the borough of Brooklyn, Gordon showed a fetal death rate of 18.7 per cent following extraction.

Material

A personal series of sixty consecutive cases of primary breech presentation, fifty-five of which were delivered vaginally, is presented as a further evidence of the benefits of a conservative policy in management. There were thirty-seven primiparas in the latter group. Since the purpose of the study was to determine the essential hazard to the child solely as a result of breech delivery, it does not include premature babies of less than 2,500 Gm. in weight. As emphasized by Beck and Philpott, the risk to premature infants in breech delivery is considerable because of the relative disparity in the diameters of the body and head. However, since maternal toxemia, atelectasis, and other conditions incident to prematurity may be associated, it is often difficult to determine exactly the deciding factor in the fetal mortality. Twin babies were excluded, since the second twin, when presenting by the breech, has its passageway already prepared. Gross monstrosities incompatible with continuing fetal life are excluded. Otherwise, the group represents the writer's total experience with breech delivery in private practice extending over a period of ten years. Cases of internal podalic version and extraction not being primary breech presentations are omitted. It has been the general policy (especially in the earlier years of practice) to make at least one attempt at external version when a breech was discovered during antenatal examination, otherwise this small series would have been considerably larger. In a few instances, however, the discovery of the presentation came as a surprise when the mother was seen in early labor. As it stands, the series reflects the experience of an average obstetrician in private practice following a definite plan of noninterference in labor in so far as possible. That an element of good fortune may have been associated with the results is freely admitted, and it is quite possible that a larger experience may show a higher fetal mortality rate.

Because of its small size, the personal study is supplemented by a similar review of the uncomplicated breech deliveries occurring consecutively in the Vancouver General Hospital from Jan. 1, 1945, to June 30, 1946, inclusive.

TABLE I. INCIDENCE OF BREECH CASES AT VANCOUVER GENERAL HOSPITAL
(JAN. 1, 1945, TO JULY 1, 1946)

1. Viable births	5987
2. Total breech cases	224 or 3.8%
3. Uncomplicated breech deliveries	145 or 2.6%
(Twins, monstrosities, less than 2,500 Gm. excluded)	

While many of the cases in the latter series were delivered by specialist members of the attending staff, fully 60 per cent of them were under the care of various general practitioners of the visiting staff or were delivered by interns in training. The over-all group is, I believe, sufficiently large to indicate the general character of the fetal results in breech delivery at the Vancouver General Hospital.

The outcome for the child in the two series is shown in Table II.

In guiding the head through the pelvis the widest available diameters as determined by x-ray pelvimetry should be considered. I have had no experience with the Burns-Marshall technique of allowing the child to hang by the head so as to draw it into the pelvic cavity, but its enthusiastic recommendation by British obstetricians would suggest its use when necessary.

In delivery of the shoulders, arms, or head, I am convinced that it is a mistake to adhere rigidly to a planned routine in the face of an apparently conflicting mechanism. One must adapt the procedure according to circumstance.

Discussion

Many talks with younger practitioners on the subject of breech presentation has led one to the conclusion that there exists a considerable fear of the "breech birth" in the mind of the profession at large based upon the serious prognosis for the child. This exaggerated dread may express itself by too strenuous attempts at external version, by excessive haste or roughness in delivery, or by a frequent recourse to cesarean section.

The merits of external version when gently performed have been repeatedly attested, and it is far from my intention to question its value. Nevertheless, it is often most difficult of accomplishment, in the very instances where it would be highly desirable, namely, in primiparas where not infrequently a tense abdominal wall or engagement of the breech may prevent its performance. It would seem that the hazard of breech delivery is not sufficiently great to justify too vigorous or persistent attempts at external version in difficult instances, nor in particular to warrant its employment under anesthesia. An increasing number of cases of placental separation and other accidents are being reported.

The pharmacologic method of version during pregnancy by means of purgation as recommended by certain Spanish-American obstetricians is interesting and harmless and deserves more widespread clinical trial.

When we consider cesarean section, it is apparent that abdominal delivery must have wider application in breech presentation than in vertex cases. Since disproportion may not become evident until the aftercoming head reaches the midpelvis, trial labor is of little value. There is, moreover, no time for head molding. Careful clinical and radiologic examination of the maternal pelvis should generally indicate the way to safety. Even with the normal pelvis, the hazard to the overlarge child (of more than 4,000 Gm.) is to be remembered, especially in elderly primiparas. However, breech presentation as such should not be considered an indication for cesarean section except when the pelvis is contracted or under other unusual circumstances.

In this connection it is well to re-evaluate the slow labor in primiparas after a test of from twelve to eighteen hours. Ineffectual uterine contractions with a prolonged and that the risk to the child will be increased proportionately. thick, slowly dilating cervix will generally indicate that the labor will be unduly. Delivery by cesarean section may be the best solution in some of these cases.

Summary and Conclusions

Belief is expressed that a more favorable fetal mortality rate than generally quoted is possible, based upon the following considerations:

TABLE IV. DETAILS OF PERSONAL SERIES

C. <i>Average Duration of Labor</i>		
Primiparas	20 hours	
Multiparas	6 hours	
D. <i>Average Weight of Child</i>		
For Primiparas	3,342 Gm.	
For Multiparas	3,516 Gm.	
E. <i>Greatest Weight of Child</i>		
For Primiparas	4,290 Gm.	
For Multiparas	4,050 Gm.	

TABLE V. PERSONAL BREECH CASES DELIVERED BY CESAREAN SECTION

NO.	AGE	PARA	PELVIS	X-RAY	TRIAL LABOR	WEIGHT OF CHILD	REMARKS
1.	25	0	Android	Yes	None	3,010 Gm.	Marked contraction of midpelvis
2.	27	0	Gen. contracted	Yes	None	3,150 Gm.	-----
3.	27	0	Android	Yes	None	3,460 Gm.	Very small outlet
4.	32	0	Android	Yes	None	2,965 Gm.	Small mid-pelvis
5.	33	0	Normal	Yes	24 hours	3,655 Gm.	Cervical dystocia

Careful and frequent auscultation of the fetal heart is practiced throughout the second stage of labor so that an immediate extraction may be undertaken should fetal distress appear. If this precaution is observed, the stage of expulsion may be extended beyond the traditional two or two and one-half hours without anxiety if progress is being made. A too prolonged second stage, however, may favor the development of a contraction ring. The practice of "breaking up the breech" by bringing down a foot by Pinard's maneuver was rarely followed, it being considered preferable to perform complete extraction under full anesthesia if failure of advance occurred in the second stage of labor with the breech high.

When the perineum becomes distended, a pudendal nerve block anesthesia is induced using 1 per cent procaine solution containing three minims of epinephrine to the ounce. In a few minutes the pelvic floor may be painlessly dilated, if desired, by the familiar "ironing-out" maneuver. A wide episiotomy is then made, following which descent and delivery of the breech usually occur promptly. After the birth of the umbilicus, complete general anesthesia is induced and the anesthetic agent must act rapidly. A slowly acting anesthetic such as ether may be worse than none. As the anterior scapula presents, it is pushed toward the fetal spine as recommended by Potter, thus delivering the anterior arm. Should the anterior shoulder not appear promptly or the anterior arm be extended, the child's body is drawn slightly downward and rotated so as to make the posterior shoulder become anterior by the method so well described by Löwsett, though probably practised by obstetricians for many years. The rotation is then reversed to deliver the other arm. One trial is made to deliver the head by the modified Wigand-Martin maneuver. If easy delivery is not forthcoming, forceps are promptly applied. Whatever method is employed for the delivery of the head, flexion by jaw traction with rotation under the pubic arch is maintained so as to roll the head slowly out of the pelvis. General anesthesia is discontinued with the birth of the head, and the episiotomy repaired at leisure while the local anesthesia is still effective.

In his management Dr. Trites is conservative. The mother's forces are utilized to the full, and he interferes only when there is failure of progress. This wise restraint is the more admirable in that it calls for a minimum of general anesthesia and for no unusual dexterity on the part of the operator.

DR. WM. A. SCOTT, Toronto.—I do not use spinal anesthesia as a routine in obstetrics, but have adopted it to a greater extent than in the past. I use a low spinal anesthesia in all breech deliveries at or near term, and also when I anticipate a difficult operative delivery in a vertex presentation. The anesthetic need not extend to any great height, and it gives a relaxation of the soft tissues that facilitates all operative procedure.

I should like to ask Dr. Trites just what advantages a local, supplemented by a general anesthetic has over a low spinal anesthesia.

Dr. Trites laid down the dictum that a careful radiologic study of the pelvis would determine those cases where, because of pelvic disproportion a cesarean section is indicated. I would like his opinion on a somewhat controversial point. In an elderly primipara in whom there is no disproportion, with a breech presentation and extended legs, one anticipates a difficult delivery. Under such circumstances is one not justified in doing a cesarean section in the interests of the child?

DR. B. P. WATSON, New York.—We have for many years at the Sloane Hospital carried out a very conservative policy in breech delivery. Our teaching has been that practically every breech should deliver spontaneously. Full dilatation of the cervix and stretching of the pelvic floor is allowed to occur by the breech itself. The frank breech is not broken up unless descent is arrested.

The greatest aid in reducing fetal mortality is episiotomy. This should be done as soon as the breech begins to stretch the perineum. It should not be deferred until after the breech has been born and difficulty with the aftercoming head is encountered. When we follow these rules we do not fear a breech delivery anymore than we do a vertex.

DR. TRITES (Closing).—It was gratifying to note that Dr. Mitchell shares my feelings with respect to breech presentation, and I should like to congratulate him on his results. I have had no experience with the use of the Voorhees' bag in breech cases, but I believe that it might have a place when the cervix was dilated to 4 or 5 cm. and progress slow. Here it might be used to advantage.

In replying to Dr. Scott, I have had no experience with spinal anesthesia in delivery, but am assured that it gives excellent relaxation of the pelvic floor, and I believe it might be of special use in certain cases. The particular advantage of local anesthesia is that the patient may use her voluntary powers up to the time of actual delivery. There is also the question of the availability of trained anesthetists, which was until recently a constant difficulty in the hospital where I work. Dr. Scott mentioned the question of elective cesarean section in the elderly primipara with a frank breech presentation and a normal pelvis. It is quite true that the risk to the child may be increased because of the patient's age. In deciding on the method for delivery, I would be guided by two or three factors—first, the estimated size of the child, and secondly the condition of the cervix. If the cervix were soft and well effaced when labor commenced, the child not obviously overlarge, and the breech well engaged, I would give such a patient a test of labor to judge her progress with the thought that I could change my method of delivery at the end of twelve hours, if considered advisable.

Replying to Dr. Grant, his question is well taken regarding the necessity of "ironing-out" the perineum before delivery. One of the advantages of local anesthesia is that the pelvic floor will be relaxed, and in the average patient there will not be much need to do any ironing-out; although, at times it is helpful to do so when the patient has a rigid levator ani muscle.

I am grateful to Dr. Watson for his support of the conservative method of treatment, and agree fully that episiotomy should be done early, well in advance of the birth of the breech.

1. A complete study of the maternal pelvis by clinical and radiologic methods with delivery by cesarean section if the pelvis is contracted.
2. A conduct of labor designed to achieve a high incidence of spontaneous delivery of the breech with interference only on definite indication.
3. Constant personal supervision of the second stage of labor by the attending obstetrician.
4. The utilisation of local anesthesia, wide episiotomy, and frequent application of aftercoming head forceps in delivery.

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Discussion

DR. ROSS MITCHELL.—In his well-reasoned paper Dr. Trites shows that the prevalent gloom in breech presentation is unjustified, and that the risk to the fetus in primary breech presentations can be much less than is usually stated. Probably it is no greater, and may be even less than for occiput posterior positions. Personally, the latter have given greater worry than breech presentations.

The bugbear of disproportion can be obviated by careful clinical observation, supplemented when necessary with x-ray examination. The incidence of cesarean section need not be high. Dr. Trites presents from his own practice sixty consecutive cases of primary breech presentation with five abdominal deliveries. In my own practice from July 1, 1936, to the present date there were fifty-six cases of primary breech presentations at term or near term with two abdominal deliveries. The combined groups may be presented thus:

<i>Method of Delivery</i>			
Vaginal deliveries	109	Cesareans	7
<i>Vaginal Deliveries</i>			
Primiparas	73	Multiparas	36
<i>Fetal Mortality in Vaginal Delivery</i>			
Total	109	Stillbirths, 1 Neonatal Death,* 1 fetal mortality, 1.72%	

In my own series of fifty-four deliveries there were four babies weighing 9 pounds 11 ounces; 9 pounds 10 ounces; 9 pounds 3 ounces; and 9 pounds 2 ounces, respectively, and a total of eight weighing $8\frac{1}{2}$ pounds (3,800 Gm.) or over. The management of delivery was substantially that advocated by Dr. Trites. I can emphasize the value of local anesthesia, of deep episiotomy and of not hurrying the head through the birth canal.

* (Congenital heart) Corrected mortality 0.86 per cent.

A laparotomy was performed and the mass was found to be situated in the location of the right ovary and obviously containing the pregnancy. The omentum and small bowel were adherent to the mass. After freeing of adhesions the mass was seen connected to the uterus by the ovarian ligament, which was enlarged. The uterus was slightly enlarged, and retrodisplaced in the cul-de-sac. Both tubes were lying free and looked normal. The left ovary was cystic, about the size of a lemon, lying free in the left fossa. The right ovary containing the

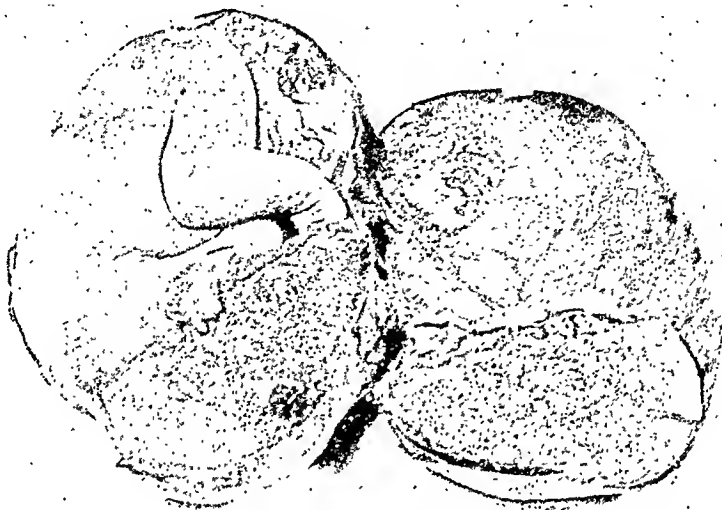


Fig. 1.—Specimen opened showing surrounding capsule of ovarian tissue.



Fig. 2.—Section of capsule showing ovarian tissue and gland suggestive of endometrial glands.

pregnancy and the left ovary containing the cyst were removed. The post-operative course was uneventful, and she was discharged on the thirteenth day.

Pathologic Report.—The specimen consisted of a large ovarian tumor, measuring 19 by 13 by 9 cm., and weighing 1,300 grams. The external surface was smooth and glistening. On section, the tumor was found to contain a large fetus

OVARIAN PREGNANCY*

R. T. WEAVER, M.B., D. L. ADAMSON, M.D., AND F. L. JOHNSON, M.D.,
HAMILTON, ONTARIO

(From the Department of Obstetrics and Gynaecology, Hamilton General Hospital)

MRS. I. M., a 42-year-old white female, entered the Hamilton General Hospital Sept. 17, 1945. At that time she complained of "no periods for twelve months."

Her last normal menstrual period was Sept. 1, 1944. She had slight nausea with occasional vomiting in October, 1944, which only lasted for approximately two weeks. She visited her doctor in November, 1944, at which time a diagnosis of pregnancy was made. She did not return as she felt perfectly well. She was never aware of any abdominal enlargement or pressure of abdominal mass, nor did she feel any fetal movements. She continued well until April, 1945, when she began to have pains around the level of the umbilicus accompanied by marked constipation, and "a lot of gas." This lasted for approximately one week, during which time she was very tired.

From the middle of May to the middle of June, 1945, she had intermittent spotting of blood from the vagina accompanied by small clots which lasted five days. There was no bleeding since that time. She had intermittent pain in the right lower quadrant for two weeks, which would disappear with rest.

In August, 1945, she was examined regarding accepting steady employment. At this time she was referred for x-ray examination of the abdomen. The report was as follows:

A film of the abdomen showed the presence of a single fetus of approximately five months. The midpoint of the head was at the level of the posterior iliac crest on the right side. There was overriding of the fetal skull bones, breech presenting, spine to the left. No placenta could be identified with any certainty as such, and the total mass was rather smaller than one would anticipate in consideration of the various elements contained in a pregnant uterus. No abdominal masses other than this pregnancy were identified.

Hospitalization was advised but she did not report for another month.

She had two previous normal pregnancies and deliveries twenty-four and twenty-two years ago.

No abnormalities were present until the onset of her present illness.

Physical examination on admission showed her blood pressure to be 124/82; temperature 98.2° F.; pulse 70; respiration 18; red blood cells, 5,400,000; white blood cells 8,000; hemoglobin 97 per cent.

Urinalysis and blood chemistry normal.

Examination essentially normal except for abdomen and pelvis.

There was a firm mass, size of football, rising from pelvis to just above level of umbilicus lying more to the right than to the left side. There was no tenderness, and the mass seemed partially moveable. The cervix was firm, elongated, and closed. It was thought that the uterus could be palpated in the cul-de-sac, and this mass was probably extruterine.

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Original Communications

IN VITRO FERTILIZATION AND CLEAVAGE OF HUMAN OVARIAN EGGS*

MIRIAM F. MENKIN, M.A.,† AND JOHN ROCK, M.D., BROOKLINE, MASS.

(From the Department of Gynecology, Harvard Medical School, and the Fertility Clinic Laboratory, Free Hospital for Women)

IN 1880, S. L. Schenk,¹ a Viennese embryologist, reported in some detail his experiments on in vitro fertilization of the ovarian eggs of the rabbit and the guinea pig. He described the first cleavage, as it occurred in vitro, and noted the inequality in size of the two resulting daughter cells. Some years later, Onanoff,² in a brief note published posthumously in 1893, mentioned that he had been able to induce in vitro fertilization and cleavage of uterine eggs of the rabbit and the guinea pig. He stated that the eggs had developed in vitro up to the eight-cell stage. Furthermore, this author reported that when ova fertilized in vitro were transferred to the abdominal cavity of another animal, whether male or female, of the same species, development continued until the embryos had attained the stage of the primitive streak. No details or photographs were furnished in connection with these experiments, nor has a careful survey of the literature discovered confirmation of these results by other investigators.

In 1930, Pincus³ observed sperm penetration in tubal rabbit eggs inseminated in vitro. By transplantation of such eggs into the oviduct of a pseudopregnant rabbit which subsequently produced young, possessing the proper genetic characteristics, Pincus and Enzmann⁴ in 1934 presented what they regarded as the "first certain demonstration that mammalian eggs can be fertilized in vitro." In the same year, Krassovskaja⁵ reported continuous observations for many hours of in vitro fertilized tubal rabbit eggs. Forty-six hours after spermatozoa had been added to the egg, this author noted the development of the morula stage (twenty-eight cells). Subsequently, this same investigator⁶ described in vitro fertilization and cleavage of tubal rabbit eggs that had been inseminated with rat spermatozoa.

In 1935, Pincus and Enzmann⁷ transplanted into the Fallopian tubes of pseudopregnant rabbits ovarian eggs that had been inseminated in vitro. Two to three days later, regular cleavage was observed to have occurred in a small number of cases. Consequently, these investigators concluded that "normal fertilization can be secured with eggs removed from the follicles." As a final proof that true fertilization of mammalian ovarian eggs can occur in vitro, Pincus⁸ in 1939 demonstrated that some ovarian rabbit eggs that had been exposed to spermatozoa in vitro possessed the diploid number of chromosomes.

Early cleavages in vitro have been observed in rabbit eggs that had been fertilized in vivo. Lewis and Gregory⁹ obtained cinematographs of such eggs as they developed from the one- to the eight-cell stage. In the guinea pig, Squier¹⁰ reported in vitro cleavage from the two- to the four-cell stage of four eggs that had been fertilized in vivo.

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†Present address: Lankenau Hospital Research Institute, Philadelphia, Pa.

measuring from vault to coccyx 21 centimeters. Lying at the opposite end of the tumor and just beside the fetus, to which it was joined by the umbilical cord, was a placenta measuring 10 by 5 centimeters. Both fetus and placenta were encapsulated by a very thin wall, the inner lining of which was fairly smooth. The average thickness of the wall was $1\frac{1}{2}$ millimeters. The fetus was well formed, and showed no gross abnormalities.

Sections of the other ovary which measured 6 by 5 by 4 cm. showed it to be cystic and thin-walled. It was found to be filled with clear serous fluid. The inner lining of the cyst was smooth and glistening. To one side could be seen a small portion of tissue which appeared to be atrophic ovarian tissue.



Fig. 3.—Section of capsule showing ovarian tissue and corpus albicans.

Microscopic.—Sections of the wall showed it to be composed of typical but compressed ovarian stroma containing a compressed corpus albicans. On the inner surface of one section could be seen numerous fragments of hairs embedded into the ovarian tissue. The surrounding tissue showed foreign body giant cell reaction. This portion of the wall unquestionably contained ovarian tissue. Repeated sections through the wall of the tumor showed the complete absence of epithelial lining and the constant presence of ovarian stroma. Some sections showed several glands lined by cuboidal and columnar epithelium. Sections of the other cyst showed it to be lined with very flattened epithelium which has ovarian stroma along one area.

Pathologic Diagnosis.—(1) Ovarian pregnancy, and (2) serous cyst of left ovary.

The patient was seen in the office six months later. She had had no bleeding since discharge from the hospital and was feeling well. Examination revealed nothing of note at this time.

It is felt this case meets all the criteria of true primary ovarian pregnancy.

similar stage, but part of the cytoplasm appeared fragmented, and soon proceeded to undergo rapid, degenerative changes. In this report, as in the preliminary one,²⁰ we will therefore confine our discussion to the two eggs in the two-cell stage and the more normal appearing of the two eggs in the three-cell stage.

The Two-Cell Stage of the Human Egg

First Specimen.—The first specimen was obtained from a 38-year-old married woman (No. 20,768) who had had four labors, and was admitted to the hospital with a diagnosis of relaxed perineum, lacerated, cystic, eroded cervix, and prolapse. At operation, on the tenth day of the cycle, a complete hysterectomy and right salpingo-oöphorectomy were performed. Cycles immediately preceding operation had been, respectively, twenty-seven, twenty-three, forty-seven, and twenty-eight days. The endometrium was found to be in the late proliferative stage.

The egg was recovered free in the follicular fluid drained from a bluish follicle, 2.3 cm. in diameter, in the extirpated right ovary, about one hour after oöphorectomy. When first observed, the ovum was within a moderate investment of granulosa cells. After rapid transfer through three portions of sterile Locke's solution, it was pipetted into a Carrel flask containing 3 c.c. of serum prepared from the blood of the egg donor.* The blood had been taken from the patient after the operation. The egg was then placed in the incubator at 37.5° C. It had been at room temperature for about three hours; i.e., the time elapsing since oöphorectomy.

After twenty-seven hours of culture, the preparation was removed from the incubator and examined. The compact granulosal investment, which had surrounded the egg on the previous day, now appeared as a loose meshwork of shrunken, degenerated, granulosa cells. The egg was rapidly transferred through small amounts of Locke's solution in three watch glasses. In the third watch glass were then pipetted a few drops of the so-called "fertilizing suspension" of spermatozoa. This had been prepared as follows:

Seven-tenths of 1 c.c. of a semen specimen one and one-half hours old (in which 95 per cent of the spermatozoa were highly motile) was pipetted into a centrifuge tube and the volume brought to 2 c.c. with sterile Locke's solution. After being mixed, the suspension was centrifuged for fifteen minutes at full speed.† The supernatant fluid was then decanted, and to the firm white sediment was added Locke's solution, again to a volume of 2 c.c. The sediment was diffused in the medium by gently drawing the former in and out of a pipette. Centrifugalization and decantation were repeated, and then to the washed sediment was added Locke's solution to a volume of 0.2 c.c.; i.e., about one-third the original volume of the semen used. A hanging-drop of this suspension showed high concentration and activity. At the time when the spermatozoa were added to the egg, the former had been at room temperature for two hours and forty-five minutes; i.e., the interval since ejaculation.

The watch glass containing the ovum and spermatozoa was left on the stage of the dissecting microscope at room temperature for one hour, the egg being kept in constant view (at a magnification of $\times 35$). The spermatozoa showed great activity throughout the period of observation; they were clearly seen to travel through the interstices of the loose cellular formation surrounding the egg, and many were noted in active motion around the zona pellucida.

*In all the experiments reported here, the serum used for culture of the eggs prior to exposure to spermatozoa was that of the patient who had furnished the eggs, while subsequent culture (following contact with spermatozoa) was carried out in serum of any patient willing to donate blood.

†About 3,500 revolutions per minute; an International Clinical Centrifuge with a No. 804 angle head was used.

In vitro insemination experiments have also been performed with eggs of the mouse and rat.^{11, 12} While certain effects of spermatozoal action were noted, such as dehiscence of follicle cells (in both mouse and rat eggs), as well as shrinkage in volume of the egg and second polar body formation (in the rat egg), cleavage was not reported in these studies.

In vitro cleavage of in vivo fertilized rat eggs was occasionally observed by Defrise¹³ when the eggs were cultivated in certain media. Only one or two divisions were noted. In their comprehensive monograph on the mouse ovum, Lewis and Wright¹⁴ include a photograph of an egg fertilized in vivo that divided into two cells in vitro.

To our knowledge, there have been no reports of in vitro fertilization of the eggs of higher mammals. In 1941, Lewis and Hartman¹⁵ mentioned two unsuccessful attempts to fertilize tubal monkey eggs in vitro. Previously, these same investigators¹⁶ had cultured in vitro from the two- to the eight-cell stage a monkey egg fertilized in vivo.

Most textbooks of embryology comment on our lack of knowledge of the fertilization and first cleavage stages of the human ovum. We have encountered in the literature only two references to the earliest stages of the human zygote. In 1944, Hamilton¹⁷ reported in a fresh tubal egg removed from an operative case the presence of many spermatozoa in the zona pellucida, and toward the center of the egg a clear area containing "dark rodlike bodies suggestive of chromosomes on the spindle of first cleavage." However, since this specimen was lost before fixation, there is no proof that the egg was actually fertilized. Shortly afterwards, Hamilton¹⁸ noted, in a fixed preparation of an unsegmented human tubal egg, many spermatozoa in the zona pellucida, and within the cytoplasm, two nuclei of unequal size, which he regarded as the pronuclei. This paper appeared in abstract form; so far, we have been unable to find a more detailed account.

In 1939, Pineus and Saunders¹⁹ reported that about 30 per cent of human ovarian ova cultured in blood serum for intervals ranging between eight and one-half and twenty-four hours showed polar body formation and hence became theoretically susceptible to fertilization. On the basis of these findings, we have made numerous attempts to initiate in vitro fertilization of human ovarian eggs cultured for varying lengths of time. Utilizing the surgical material available at the Free Hospital for Women, we performed most of our experiments on eggs from ovarian tissue removed just prior to the expected time of ovulation. Nearly 800 human follicular eggs have been isolated and studied during the course of this investigation; of these, 138 have been observed after exposure to spermatozoa in vitro.*

Several factors were varied through the period of this study; e.g., the conditions of culture of the eggs, both before and after exposure to spermatozoa, the duration of contact of egg and spermatozoa, and the concentration of the sperm suspensions used. Employing a certain combination of these variables, we have been able to induce cleavage in three experiments. A condensed report of these findings has been published previously.²⁰

In two of these cases (No. 20,768 and No. 14,518), the egg, after being subjected to certain procedures (to be described later), was found to be in the two-cell stage. In the third case (No. 21,012), two eggs divided. One of these, when first seen in cleavage, consisted of one large blastomere and two smaller ones, each of the three containing a round, vesicular body, which, at the time, we believed to be a nucleus. The second egg from this same patient was in a

*Most of the eggs studied were obtained by incising individual follicles, ranging in size from 3 mm. to about 3 cm. However, a few of the eggs were recovered by teasing pieces of ovarian tissue in a dish containing Locke's solution and allowing the ova to float into the surrounding fluid. The follicles from which these eggs originated were, as a rule, smaller than 3 mm. in diameter; in some cases, they were too small to be seen with the naked eye.

of cystocele, rectocele, and retroverted, prolapsed uterus. A complete hysterectomy and right salpingo-oöphorectomy were performed on the eleventh day of the cycle. The endometrium was in the late proliferative phase of its development. The last two cycles preceding operation had been, respectively, twenty-eight and thirty-four days long.

Twelve eggs were recovered from the extirpated right ovary by incising and flushing the follicles, and one from follicular fluid obtained by aspiration in situ of follicles of the left ovary. Since the follicles visible in the right ovary were closely approximated on the surface, it was not possible to identify the one from which any particular egg was derived. Although twelve eggs in all (one was lost) were carried through the entire procedure and exposed to the same technique, only one of them divided.

This ovum was one of a set of four, of which three, when first seen, were covered by a thick granulosa cell investment, and one by only a few rows of cells. The eggs were washed twice in Locke's solution, and were then transferred to a Carrel flask containing 3 c.c. of serum that had been prepared from blood taken from the egg donor twenty-two hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the eggs had been at room temperature for about three and one-half hours; i.e., the interval since oöphorectomy.

After twenty-two and one-half hours' incubation, the eggs were washed once in Locke's solution and exposed for two hours at room temperature to a sperm suspension prepared from the same donor and in essentially the same manner as in the first case reported above. At the time when the spermatozoa were added to the eggs, the former had been at room temperature for three hours; i.e., the interval since ejaculation. The ova were then washed twice in Locke's solution and transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that two hours previously had been given by a 62-year-old patient with carcinoma of the cervix uteri. The preparation was then incubated for forty-five hours at 37.5° C.

When examined at the end of the incubation period, the egg, as observed through the wall of the flask, was found to be in the two-cell stage. A photograph (Fig. 2A), made of the specimen two hours later, shows it to resemble very closely the first egg recovered in the same stage (Fig. 1A). Two "biseuit-

Fig. 1.—No. 20,768. Human egg in two-cell stage: *first specimen*. This egg was recovered free in the fluid drained from a 2.3 cm. ovarian follicle of a 38-year-old white woman after laparotomy on the tenth day of the cycle. After having been washed in Locke's solution, the ovum was cultured for twenty-seven hours at 37.5° C. in the serum of the same patient. It was again washed in Locke's solution and was exposed in vitro for one hour at room temperature to a washed concentrated suspension of human spermatozoa in Locke's solution. It was then transferred to serum from a 51-year-old female patient and incubated. After forty and one-half hours of culture, the egg was found to be in the two-cell stage, and a sketch was made of it. The specimen was then fixed, but was lost during dehydration.

A. Free-hand sketch of egg under high power of the compound microscope (after forty and one-half hours of culture).

B. Convolutd wall of mature Graafian follicle from which the egg was recovered. Insemination of the egg took place twenty-nine and one-half hours after the follicle wall was fixed. Section showing granulosa, theca interna, and theca externa. There is some focal separation (? artifactual) between the granulosa and the theca interna. In the theca interna, there is considerable vascularization and congestion. Note large, pale-staining cells of the theca interna, as contrasted with the small, polyhedral, dark-staining cells of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindrical and stellate and are separated by variable amounts of edema fluid. It appears as though luteinization had just begun in the theca interna, but not in the granulosa cells. Fixed in Bouin's solution; embedded in paraffin; sections cut at 6 μ , and stained with hematoxylin and eosin. (X400.)

At the end of one hour, the ovum, along with some of the surrounding sperm suspension, was transferred to a Carrel flask containing 3 c.c. of serum of a 51-year-old patient who had been admitted to the hospital because of dysfunctional flowing. The blood had been obtained from the patient about six hours before the egg was placed in the serum. As the egg was pipetted into the Carrel flask, the loose formation of degenerated cells surrounding it suddenly dropped off, and it appeared as a single round cell with a fuzzy border.

When it had been cultured for forty and one-half hours, the ovum was washed out of the Carrel flask into a watch glass with Locke's solution.* In the plane of examination under the dissecting microscope, it now appeared to consist of two equal, spheroid blastomeres, each measuring 86μ in diameter, and was enclosed within a zona pellucida of uniform thickness, measuring 14μ .

A sketch of the egg was made under the compound microscope (Fig. 1A). Now the blastomeres appeared elliptic. At this time, a slight inequality in size of the blastomeres was noted. The ovum was then gradually fixed in Bouin's fluid by removing the surrounding medium (Locke's solution) and substituting the fixative, drop by drop. Fifteen minutes after the start of fixation, the ovum had undergone considerable shrinkage (to almost one-half its original volume). Dehydration had nearly been completed when the egg, unfortunately, was lost.

The Follicle Wall.—For several reasons, it seems worth while to include in this report a photomicrograph of the stained section of the follicle from which this egg was obtained (Fig. 1B). In the first place, it is the only one in our large collection of so-called "preovulatory" human follicles which we are certain contained a fertilizable ovum at the time the section was taken; i.e., it is the only section in existence, as far as we know, of a human ovarian follicle which can be exactly dated with respect to subsequent fertilization of the egg derived from it. The time interval between fixation of this follicle and insemination of the egg was twenty-nine and one-half hours.

In section, the convoluted wall of this follicle shows the three typical layers: granulosa, theca interna, and theca externa. The inner, or granulosa layer, is composed of small, polyhedral, dark-staining cells in which mitoses are prominent. The basal layer is more closely packed and the nuclei are more cylindric with their vertical axes arranged perpendicularly to the follicle wall. There is some focal separation (?artifactual) of the granulosa and theca interna. The latter is well vascularized, congested, and composed of cells which are larger, paler and more irregular than those of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindric or stellate and separated by variable amounts of edema fluid. It appears as though luteinization has just begun in the theca interna, but not within the granulosa cells. Apparently, then, this follicle represents a typical "preovulatory" stage; i.e., a mature follicle that is just about to rupture.†

Second Specimen.—Of the second egg in the two-cell stage we have a complete series of stained sections. Essentially the same procedure as described above was carried out on an ovum, washed from a follicle of a 31-year-old para vi, gravida viii (No. 14,518), who was admitted to the hospital with a diagnosis

*According to our usual technique, the eggs are pipetted out of the Carrel flask. In this case, however, it was not possible to identify the egg through the wall of the flask, as some contamination of the medium had occurred, probably due to the fact that in transferring the egg to the Carrel flask part of the sperm suspension had been carried along with it. Contamination of the medium was also noted in the third experiment to be described, where the same procedure was followed, but not in the second experiment. In the latter case, the egg was washed several times before transference to fresh serum.

†We are indebted to Doctor Arthur T. Hertig for this description of the histology of the follicle wall.

shaped"* blastomeres of slightly unequal size, containing granular cytoplasm, are enclosed within the zona pellucida. Numerous spermatozoa are present, some along the border and at least one within the zona.

The entire egg (including the zona pellucida) measured 153μ by 155μ ; the vitellus was 100μ by 113μ , and the average thickness of the zona pellucida was 23μ . The blastomeres measured 88μ by 58μ , and 105μ by 58μ , respectively.†

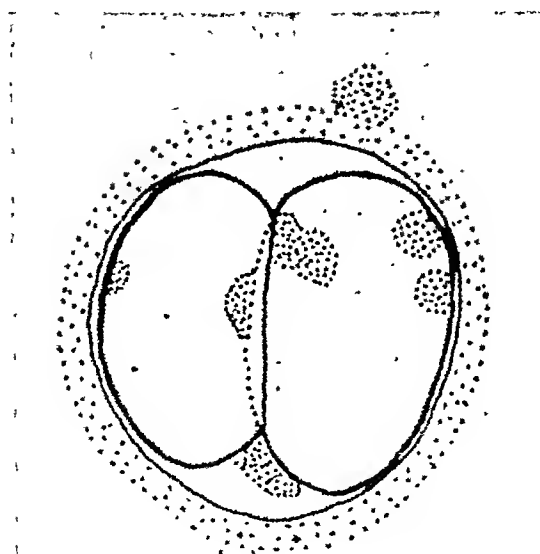
The egg, transferred to a plasma drop, was fixed according to the method described by Pineus.⁸ The plasma drop was warmed for one-half hour under an electric light bulb. The resulting clot was then carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ , and stained with hematoxylin and eosin.

Since the ovum is included in eight sections, its total thickness after fixation is approximately 64μ . A section through the middle of the specimen (Fig. 2B) measures 50μ by 75μ (excluding the imperfect zona). The blastomeres (designated, for convenience as "A" and "B," from left to right) measure 63μ by 39μ , and 66μ by 36μ , respectively. The cytoplasm appears uniformly granular, with the exception of the polar regions where there is beginning vacuolization, as had been noted in the fresh specimen immediately following photography. In the approximate center of each cell, there is a round, vesicular nucleus containing a chromatin meshwork. The nucleus in blastomere "A" measures 18μ by 13μ , and that in blastomere "B," 16μ by 15μ . The zona pellucida surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona pellucida in section was doubtless due to the method of fixation; as seen in Fig. 2A, it had been intact in the fresh specimen. In a clearly defined portion (near "1 o'clock"), the zona measures 7μ to 8μ across. Several dark bodies suggestive of sperm heads may be identified on the photograph; one of them appears to be just within the cell body of blastomere "B" (near "1 o'clock").

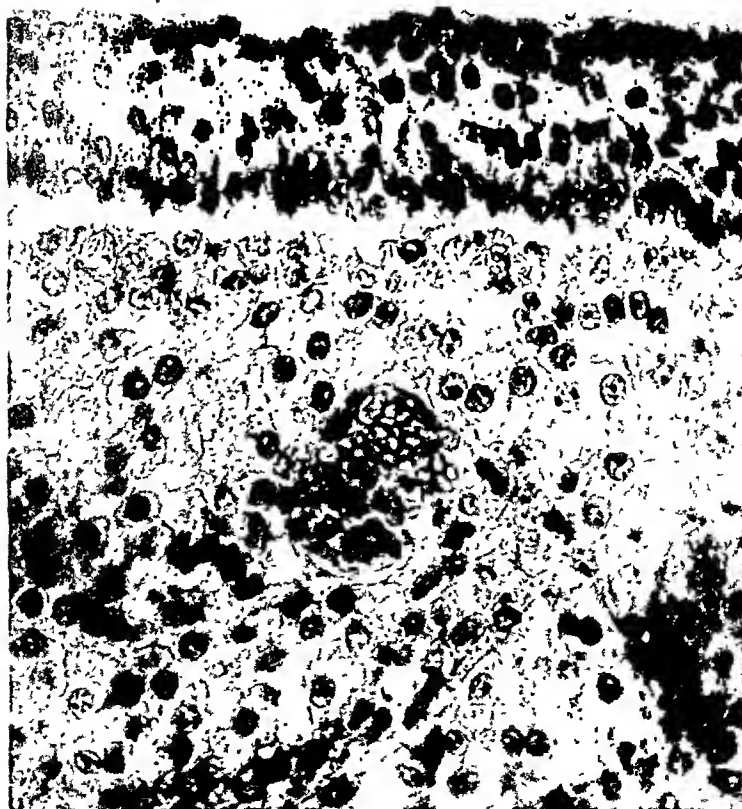
The section adjacent to the one described above, and represented in Fig. 2C, was, unfortunately, torn during cutting and is reproduced only to show the polar body near "11 o'clock," beside blastomere "A." The polar body measures 18μ by 10μ , and contains what appears in the photograph as a group of chromatin units discrete enough to be counted. However, when the photograph is magnified twelve times, we see the chromatin in the form of a lobulated body, only two clumps being definitely separated from the general mass. Opposite blastomere "B" (at about "3 o'clock") two dark bodies resembling sperm heads are seen. Other sections of this egg show one, five, seven, and nine such bodies, respectively.

*The so-called "biscuit" shape is characteristic of the blastomeres of other mammalian eggs in the two-cell stage.¹⁰ Inequality of the daughter cells during early cleavages has been noted in the monkey egg,¹⁰ as well as in the eggs of the rabbit and guinea-pig,¹ the rat,¹² the mouse,¹¹ and other mammals.²¹ The larger cell divides first, thus accounting for the occasional finding of an egg in the three-cell stage, as shown in Fig. 3.

†In both this specimen and in that of the three-cell stage (to be described below), the sum of the dimensions of the individual components of the egg in each diameter, as listed, does not equal the dimensions of the egg as a whole in that particular diameter. There are two reasons for this discrepancy. First, the measurements in each diameter of the vitellus and of the individual blastomeres were taken through their respective centers, rather than through the middle of the egg as a whole; i.e., along a slightly different axis. This was done in order to compare the dimensions of the fresh with the fixed preparation of each egg; in neither of the fixed preparations was the egg surrounded by an intact zona. The numerical discrepancy noted here is also due in part to the presence of a shrinkage space (perivitelline space) between the vitellus and the zona. The failure of the vitellus to fill the entire zonal cavity is characteristic of other mammalian eggs after ovulation.¹⁵



A.



B.

Fig. 1.—(See legend on opposite page.)

The entire egg (including the zona pellucida) measured 170μ by 183μ ; the vitellus was 103μ by 127μ , and the zona pellucida averaged 21μ in thickness. The largest blastomere measured 97μ by 73μ , and the two smaller ones, 62μ by 62μ , and 50μ by 63μ , respectively.

The ovum was fixed, serially sectioned, and stained in the same manner as the second egg, described above. Since it includes ten sections, cut at 8μ , the specimen is approximately 80μ thick, again a shrinkage of about 50 per cent, attributable to fixation. A section through the middle of the egg measures 50μ by 86μ (Fig. 3B). The largest blastomere is here seen to measure 66μ by 49μ , and the two smaller ones, 35μ by 38μ , and 33μ by 44μ , respectively. Several round bodies are noted in the largest blastomere. These are shown more clearly in another section (Fig. 3C) in which they are seen to be present in each of the three blastomeres. They are probably nucleoli, similar to those observed in the corresponding stage of the mouse egg fertilized in vivo (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15).

In a third section (Fig. 3D), there is a structure at "11 o'clock," measuring 14μ by 9μ , which is strongly suggestive of a polar body. Nowhere throughout the preparation is there any sign of the zona pellucida; this had evidently been dissolved by the fixative.

Comparison of Two- and Three-Cell Human Eggs With Similar Stages of Other Mammalian Eggs

In regard to the duration of early cleavage stages, it is pertinent to cite the report of Lewis and Hartman¹⁶ on the culture in vitro of the monkey egg fertilized in vivo. In their experiment, in which fertilization was believed to have occurred soon after ovulation, the minimum duration of the one- and two-cell stages was thought to be thirty-six and one-half hours. We observed two eggs in the two-cell stage forty and one-half and forty-five hours, respectively, following contact with spermatozoa. Since, in the monkey egg studied

Fig. 2.—No. 14,518. Human egg in two-cell stage: *second specimen*. This egg was washed out of an ovarian follicle of a 31-year-old white woman after laparotomy on the eleventh day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum for twenty-two and one-half hours, was again washed in Locke's solution, and was exposed in vitro for two hours at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then washed in Locke's solution and incubated for forty-five hours at 37.5°C . in serum from a 62-year-old female patient.

A. Photograph of egg (after forty-five hours' incubation) showing two blastomeres within zona pellucida. At the margin of the latter are numerous spermatozoa, and at least one is seen within the zona. The entire egg (including the zona pellucida) measured 153μ by 155μ ; the vitellus was 100μ by 113μ , and the average thickness of the zona was 23μ . The blastomeres measured 88μ by 58μ , and 105μ by 58μ , respectively. ($\times 200$.) (Cf. Lewis and Hartman¹⁶—Plate 1, Fig. 7, and Lewis and Wright¹⁴—Plate 1, Fig. 10, for similar stages of monkey and mouse egg, respectively.)

B. Section through the middle of the egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was dried by warming it under a lamp. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ , and stained with hematoxylin and eosin. Two blastomeres (one slightly larger than the other), containing granular cytoplasm, are enclosed within a zona pellucida which surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona in section is ascribed to the method of fixation. Several dark bodies suggestive of sperm heads may be identified; one of them appears to be just within the cell body of blastomere "B" (near "1 o'clock").

Since the egg is included in eight sections, its total thickness after fixation is ca. 64μ . This section, excluding the imperfect zona, measures 50μ by 75μ . The blastomeres, designated, for convenience, as "A" and "B," from left to right, measure 63μ by 39μ , and 66μ by 36μ , respectively. The nucleus in "A" measures 18μ by 13μ , and that in "B," 16μ by 15μ . In a well-defined portion (near "1 o'clock"), the zona measures 7μ to 8μ across. ($\times 600$.)

C. Another section of the same egg, adjacent to the one described above. This section, torn during cutting, is reproduced to show (besides blastomere "A") a polar body, measuring 18μ by 10μ , and containing chromatin units, two of which are clearly demarcated from the general mass. ($\times 500$.)

The Three-Cell Stage

The third experiment to be reported was performed on ova of a 38-year-old patient (No. 21,012), in whom the diagnosis of tuberculous endometritis had been made after routine biopsy taken in the course of an investigation for sterility. Operation, which consisted of complete hysterectomy, right oöphorectomy, and bilateral salpingectomy, was performed on the twelfth day of the cycle. The endometrium was found to be in the late proliferative stage. The two cycles immediately preceding operation had been thirty days long. Tissue examination showed the uterus and tubes to be extensively involved by the tuberculous process; both tubes were sealed and the fimbriae were inverted.

Four eggs, recovered in washings of incised follicles, were subjected to essentially the same procedures as outlined above. After such treatment, two of them were found in the three-cell stage.

These eggs were obtained from two medium-sized follicles in the right ovary, about four and one-half hours following oöphorectomy. After having been washed three times in Locke's solution, the ova were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been obtained from the egg donor four hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the ova had been at room temperature for about five hours; i.e., the interval since oöphorectomy.

After twenty-seven hours of incubation, the eggs were washed three times in Locke's solution and were then exposed to a sperm suspension prepared from the same donor and in essentially the same manner as in the two experiments described above. At the time when the spermatozoa were added to the egg, the former had been at room temperature for four and one-half hours; i.e., the interval since ejaculation.

After having been in contact with the spermatozoa for one hour and ten minutes at room temperature, the ova, along with some of the surrounding sperm suspension, were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been given about eight hours previously by a 53-year-old postmenopausal patient. The eggs were then incubated for forty-six hours at 37.5° C.

At the end of this period, since the ova could not be identified in the flask because of some contamination, the contained fluid was emptied into a watch glass, and sketches of the eggs were made under the high power of the compound microscope.

At this time, the more normal of the two specimens consisted of three round, regular blastomeres, two of nearly equal size, and one definitely larger. In each of them we observed a round, vesicular body which, at the time, we believed to be a nucleus. Within the next two hours, the egg, kept at room temperature, appeared distorted. At the moment, we regarded this as a degenerative phenomenon, but later we were reminded that Lewis and Hartman¹⁶ had noted such distortion in the dividing monkey egg during each of several early cleavages. A photograph of the egg (Fig. 34), taken about two hours after it had been removed from the incubator, bears a striking resemblance both to the monkey egg (cf. Lewis and Hartman¹⁶—Plate 1, Fig. 9) and to the mouse egg (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15) in a similar stage. In our human egg, as in the mouse and monkey eggs, the second cleavage plane is at right angles to the first one. The bulge at "5 o'clock" is believed to represent a polar body. The two pale round formations in the center of the egg may also be polar bodies (cf. Lewis and Wright¹⁴—Plate 2, Fig. 17). At least five dark objects assumed to be spermatozoa may be identified in the zona pellucida.

In a study of in vivo fertilized mouse eggs removed at different intervals after copulation, Lewis and Wright¹⁴ have found similar time relations to prevail: duration of one-cell stage, none to twenty-four hours; duration of two-cell stage, twenty-four to thirty-eight hours, and of three- and four-cell stage, thirty-eight to fifty hours. Hence, our findings in this respect are in general agreement with those reported for the mouse, as well as for the monkey egg. In evaluating these figures, one should of course bear in mind the probability, as pointed out by Lewis and Hartman,¹⁶ that the duration of cleavage stages is longer in vitro than in vivo.

In the rabbit, on the other hand, cleavage of the fertilized egg proceeds at a much faster rate.^{9, 22} Krassovskaja⁵ reported that the first cleavage of the rabbit egg began sixteen hours and forty minutes after spermatozoa had been added in vitro, and was completed forty-five minutes later; i.e., seventeen and one-half hours after insemination. The four-cell stage was attained twenty hours after the addition of spermatozoa to the egg. By the forty-sixth hour following in vitro insemination, Krassovskaja observed the 28-cell stage (morula). As has been noted above, our two human eggs, at a corresponding interval following insemination, had reached only the three-cell stage.

Fig. 3.—No. 21,012. Human egg in three-cell stage. This egg was washed out of an ovarian follicle of a 38-year-old sterility patient on the twelfth day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum at 37.5° C. for twenty-seven hours, was again washed in Locke's solution, and was exposed in vitro for one hour and ten minutes at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then cultured for forty-six hours in serum from a 53-year-old post-menopausal patient.

A. Photograph of the egg (after forty-six hours of culture, followed by two hours at room temperature) shows it to have undergone definite changes since it was first seen in cleavage. Shrinkage and distortion in shape occurred in the interim, as well as vacuolization of the cytoplasm. Several dark bodies suggestive of spermatozoa are well defined within the zona pellucida.

The entire egg (including the zona pellucida) measured 170 μ by 183 μ . The vitellus was 103 μ by 127 μ , and the zona pellucida averaged 21 μ in thickness. The largest blastomere measured 97 μ by 73 μ , and the two smaller ones, 62 μ by 62 μ and 50 μ by 63 μ , respectively. The bulge at "5 o'clock" probably represents a polar body (cf. Lewis and Hartman¹⁶—Plate 1, Fig. 9, monkey egg). The two round pale objects in the center of the egg may also be polar bodies (cf. Lewis and Wright¹⁴—Plate 2, Fig. 17, mouse egg). (X300.)

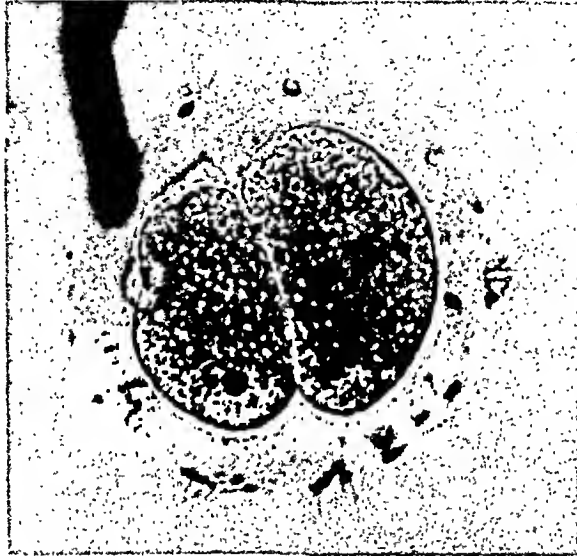
B. Section through the middle of the same egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was warmed. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8 μ , and stained with hematoxylin and eosin. Three blastomeres are well defined, the two smaller ones being nearly equal in size. Note round bodies in the largest blastomere; these are probably nucleoli (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15, mouse egg). The absence of the zona pellucida in the sections is doubtless due to the method of fixation, as it had been clearly seen in the fresh specimen.

Since there are ten sections, cut at 8 μ , the entire fixed egg is approximately 80 μ thick. This section measures 50 μ by 86 μ . The largest blastomere is here seen to be 66 μ by 49 μ , and the two smaller ones, 35 μ by 38 μ , and 33 μ by 44 μ , respectively. (X400.)

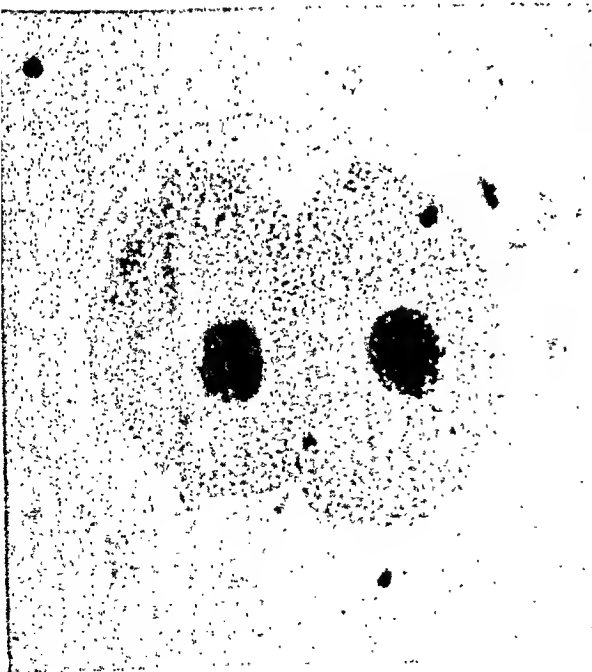
C. Another section of the same egg, showing the nucleoli more clearly. Here these appear in each of the three blastomeres. (X500.)

D. A third section of the same egg. Only two blastomeres are present in this section. An ovoid body, measuring 14 μ by 9 μ , and strongly suggestive of a polar body, is seen at "11 o'clock." (X500.)

by Lewis and Hartman, the three-cell stage lasted less than one hour, the four-cell stage began at least thirty-seven and one-half hours, and ended at least forty-six and one-half hours following fertilization. Our two eggs were seen in the three-cell stage forty-six hours after exposure to spermatozoa. As Lewis and Hartman point out, a correction of two hours should be applied to their figures, since the egg was at room temperature for this period. On the other hand, since their values are "minimum" ones, the difference in the time relations between their results and ours cannot be regarded as a significant one.



A.



B.



C.

Fig. 2.—(See legend on opposite page).

In regard to the thickness of the zona pellucida, the average value for the mouse egg, in both the two-cell stage (36 eggs) and in the four-cell stage (fifteen eggs), as computed from figures listed by Lewis and Wright,¹⁴ is 11.5μ . Calculations made from data tabulated by Lewis and Hartman¹⁵ show the average thickness of the zona pellucida in tubal monkey eggs to be 11.2μ for the two-cell stage (three eggs), and 16.5μ for the four-cell stage (two eggs). The zona pellucida in our human eggs measured 14μ and 23μ , respectively, for the two eggs of the two-cell stage, and 21μ for the three-cell egg. Whether or not these figures have any significance cannot be ascertained until more human specimens are available.

Summary

Two human ovarian eggs were found to be in the two-cell stage, and two in the three-cell stage, after in vitro exposure to human sperm suspensions, preceded and followed by culture in human blood serum. The time relations in these experiments are in general accord with those reported previously for the in vivo fertilized tubal monkey egg cultured in vitro, as well as for in vivo fertilized mouse eggs studied at different intervals after copulation.

We very gratefully acknowledge the invaluable advice and encouragement generously given us by Doctor Gregory Pincus, as well as the helpful assistance furnished at various stages by Doctor Nicholas T. Werthessen, Miss Lotte Lee Siegel, Miss Eleanor C. Adams, Mr. James M. Snodgrass, Doctor Stephen Fleck, and Doctor Harold Brown. We are also deeply indebted to Doctor Austin M. Brues for his help in the early part of the investigation, and to Doctor Arthur T. Hertig for his constant encouragement, advice, and material aid through his grant from the Carnegie Corporation of New York. We are grateful also to Doctor Warren H. Lewis of the Wistar Institute of Anatomy and Biology for reviewing this report.

The sections of two of the eggs described in this paper are in the custody of the Department of Embryology, Carnegie Institution of Washington, Baltimore, Maryland. The two-cell egg is labeled Carnegie No. 8260, and the three-cell egg is Carnegie No. 8500.1.

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It is also of interest to compare the sizes of our human eggs with those of single mouse and monkey eggs in comparable stages, as illustrated in the respective monographs of Lewis and Wright¹⁴ and of Lewis and Hartman.¹⁶ The following figures were obtained by averaging the horizontal and vertical diameters of single and similar eggs (as represented in their respective photographs).⁷

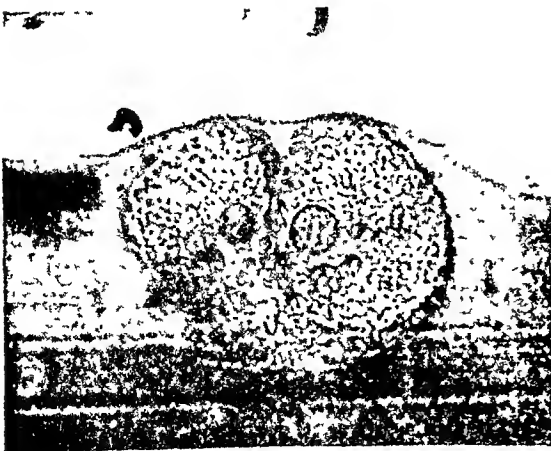
	MOUSE	MONKEY	MAN
Two-cell stage	101 μ (Plate 2, Fig. 13) ¹⁴	153 μ (Plate 1, Fig. 7) ¹⁶	154 μ (Fig. 2A, This Paper)
Three-cell stage	105 μ (Plate 2, Fig. 15) ¹⁴	145 μ (Plate 1, Fig. 9) ¹⁶	177 μ (Fig. 3A, This Paper)



A.



B.



C.



D.

Fig. 3.—(See legend on opposite page.)

*In evaluating these figures, it should be noted that appreciable variation in the size of eggs of a particular stage has been reported in several species.

Procedure and Methods

During the course of this study, vaginal smears for cytologic examination were taken on all patients admitted to the gynecologic wards, usually within forty-eight hours of their admission, care being exercised not to take smears within twenty-four hours of a vaginal douche or other procedures which might interfere with the collection of the material or staining reaction. The smears were taken by a single technician who had several years of training in this work; if any difficulties were encountered she was assisted by the resident on the service. The technique employed was essentially that described by Papanicolaou and Traut. A slightly curved glass pipette attached to a strong rubber bulb was introduced into the posterior fornix of the vagina. As aspiration was in progress the tip of the pipette was rotated into all portions of the posterior vagina in order to obtain a representative sample. When the pipette was withdrawn the secretion was blown onto the surface of two clean glass slips. The material was then further spread with the convex side of the pipette and immediately dropped into a Coplin jar containing equal parts of 95 per cent alcohol and ether, special care being taken to prevent drying before fixation. The smears were taken to the laboratory and the preparation of the slides was completed promptly, employing the techniques described by Papanicolaou. One slide was prepared with stain EA 31, and the other with stain EA 36,* since somewhat different staining reactions often afford additional information. Each slide was read at least twice, and all abnormal or unusual cells were marked with a finder for further review, if necessary. For purposes of this study it was decided to classify each slide as positive or negative and to omit the designation of doubtful for statistical evaluation. This decision was reached because in many instances it would not have been possible to obtain repeat smears because of intervening surgical procedures.

The criteria by which a slide was considered as suggestive of malignancy corresponded in general to those outlined by Papanicolaou and Traut. Emphasis was placed on abnormalities in size, morphology, and staining reaction of the nuclei. Bizarre morphology and size of the cell, abnormalities in the staining reaction, and character of the cytoplasm were considered suspicious and warranted more intensive search for abnormal cells, but a diagnosis of malignancy was not made on the latter criteria alone. The presence of red cells, histiocytes, giant cells, and increased numbers of leucocytes were almost always found in positive smears, so that their mere presence was regarded with suspicion, but these same cells may be found in benign conditions, particularly those eliciting an inflammatory response.

Each slide was marked by a number and was so reported, so that the patient and the clinical history were entirely unknown to the reader of the slides. On the other hand, the pathologic diagnosis of removed tissue was submitted by the pathologist (Dr. J. Hoffman) without any knowledge on his part of the findings of the cytologist (Dr. A. E. Rakoff). In instances where no gynecologic operative procedure was carried out, the diagnosis was established clinically. The study was continued until 500 consecutive cases had been completed.

Results

Among the 500 consecutive gynecologic patients in this study, sixty-three patients had cancer of the uterus proved by histologic examination of tissue removed by biopsy or at operation (Table I). There were fifty-seven

*These stains were generously furnished through the courtesy of the Ortho Research Foundation, Raritan, New Jersey. At present we are also using stain EA 50, which gives excellent cytologic detail.

AN EVALUATION OF THE VAGINAL SMEAR METHOD FOR THE DIAGNOSIS OF UTERINE CANCER*

LEWIS C. SCHEFFEY, M.D., A. E. RAKOFF, M.D., AND JACOB HOFFMAN, M.D.
PHILADELPHIA, PA.

WITH THE TECHNICAL ASSISTANCE OF DOROTHY MEYERS

(From the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital)

ALMOST two decades have elapsed since Papanicolaou¹ first pointed out that exfoliated cancer cells shed from a uterine malignant growth could be found and recognized in smears prepared from the vaginal secretion. It has been only in the last five years, however, that this observation has received widespread attention as a diagnostic procedure for the detection of uterine cancer. In 1943 Papanicolaou and Traut² published their monograph on the "Diagnosis of Uterine Cancer by the Vaginal Smear" based on the examination of smears from 3,014 women, of whom 179 were found to have cancer which was primary in the uterus. Much interest was aroused by this work because of the high degree of accuracy which was claimed for the method as well as the excellent descriptions and colored plates of the various cells which could be found in the vagina in normal patients, in those with various functional abnormalities, and in patients with uterine carcinoma. It was apparent from their studies that the successful application of this method necessitated considerable experience, since the cytologic changes in the cells which one might encounter in such smears are most variable. It is not remarkable therefore, that although interest in the subject has been keen, the general application of this method necessarily has been slow. The several reports which have since appeared, particularly those by Meigs and his associates;³ Fremont-Smith and associates;^{4, 5} Jones, Neustaedter, and Mackenzie;⁶ as well as Ayre,⁷ have been quite enthusiastic and have encouraged others to make use of this diagnostic aid. Our own experience with this technique is now of four years' standing, and covers approximately five thousand cases, which include patients in the gynecologic wards and clinics of the Jefferson Hospital, patients from the private practices of our staff, and from women attending various Health Maintenance and Cancer Prevention-Detections clinics throughout the city of Philadelphia. During the course of our work, the advisability of running a carefully controlled study on all patients admitted to the gynecologic wards became apparent. The purpose of this study was to determine the value of the vaginal smear as a routine procedure for the diagnosis of uterine cancer in gynecologic patients admitted to the ward.

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Read before The Philadelphia Obstetrical Society, May 1, 1947.

Review of the slides in which the diagnosis of squamous cell carcinoma had been missed showed the presence of normal cervical cells in all cases. In most of the slides in this group, the cervical cells were present in increased number, and in a high percentage there were also many red cells, histiocytes and an increased number of leucocytes. In three of the cases cervical cells were seen which were considered bizarre but not thought to be of the malignant type. These smears would ordinarily have been classified as doubtful and would have been repeated but for the specific nature of this study. In the remaining 14 cases, however, no real suspicion of malignancy was excited.

The two cases of fundal carcinoma which were missed cytologically showed increased numbers of endometrial cells with evidence of bleeding and inflammation as well. However, the cells did not present more than a normal variation in size, nor did the nuclei exhibit abnormal morphology or unusual hyperchromatic staining.

The final diagnoses based on pathologic and/or clinical findings in patients in whom the smears were incorrectly classified as positive are given in Table V.

Discussion

It is the opinion of those who have worked most with the vaginal cytology smear for the diagnosis of uterine cancer that this procedure has real merit. However the most enthusiastic workers in this field acknowledge that there are definite limitations in its application and usefulness. The warning has been stressed repeatedly that the vaginal cytology smear is not intended to replace biopsy of the cervix or diagnostic curettage of the fundus as the sole criterion for diagnosis and treatment. Even in the most competent hands it is freely acknowledged that some cases of carcinoma will be missed by the vaginal smear method and on occasion an apparent diagnosis of carcinoma will be suggested by the vaginal smear in patients subsequently proved to have nonmalignant lesions. The statistical accuracy of the procedure has been reported upon by several groups of workers. Papanicolaou and Traut² failed to detect malignant cells in the vaginal smears of patients with demonstrable carcinoma of the cervix in only four of 127 patients, and failed to diagnose carcinoma of the fundus in seven of fifty-three patients with this condition, thus giving an incidence of false negative smears for the cervical cases of 3.2 per cent, and for the fundal cases of 9.3 per cent. In 1945 Meigs³ reported a series of 1,015 cases with an over-all error of 4 per cent. In a more recent review of 1,875 cases studied in the laboratory of the Vincent Memorial (Massachusetts General) Hospital, Fremont-Smith and Graham⁵ found the procedure to have an over-all diagnostic accuracy of over 96 per cent. However, further scrutiny of their statistics shows that the percentage error in patients with proved carcinoma is considerably higher than in the negative cases. Thus, an incorrect negative diagnosis was made in 10.3 per cent of 154 carcinoma cases, while false positives were reported in 2.9 per cent of 861 negative cases, although the over-all total diagnostic error was but 4 per cent. It is apparent that the latter figure was much influenced by the high proportion of negative cases. Ayre,⁷ in a study of 580 cases, reported missed diagnoses amounting to 6 per cent in 100 patients who had a positive tissue diagnosis of malignancy. False positive smears however, occurred in only nine patients, or 1.9 per cent of the 475 who were negative for carcinoma.

patients with squamous-cell carcinoma of the cervix, five patients with adenocarcinoma of the endometrium, and one patient with a fibrosarcoma of the uterine fundus. Of the 437 patients who were classified as negative for uterine cancer, approximately two-thirds had various operative procedures which provided tissue for histologic examination. The remaining patients had various gynecologic or related conditions in which operation was not necessary for diagnosis or treatment.

TABLE I. FINAL DIAGNOSIS IN PATIENTS STUDIED

Total No. of Patients		500
Patients with Uterine Cancer		63 or 12.6%
Cervical: Squamous cell	57 or 90.5%	
Adenocarcinoma	0	
Fundal: Adenocarcinoma	5 or 7.8%	
Fibrosarcoma	1 or 1.8%	

The findings of the vaginal cytology smears with respect to cells suggesting uterine cancer are summarized in Table II. For the entire group the smear gave a correct correlation in 94.8 per cent of the cases. It will be noted at once, however, that correct results were far better for the large group of patients who did not have cancer than for the smaller group who did have a uterine malignancy (Tables III and IV). False positives occurred in seven, or only 1.6 per cent of the 437 negative patients, while the diagnosis was missed in nineteen, or 30 per cent of the sixty-three positive cases.

TABLE II. RESULTS OF SMEARS FOR ENTIRE GROUP (500 PATIENTS)

	NO.		PER CENT
Correct results	474	or	94.8
Correct positive	44		
Correct negative	430		
Incorrect results	26	or	5.2
False positive	7		
False negative	19		

TABLE III. RESULTS OF SMEARS IN CANCER PATIENTS

NO. OF PATIENTS	ENTIRE GROUP	CERVICAL CANCER	FUNDAL CANCER*
	63	57	6
Correct positive smears	44 or 70.0%	40 or 70.2%	4 or 66.7%
False negative smears	19 or 30.0%	17 or 28.8 %	2 or 33.3 %

*Including one case of fibrosarcoma, diagnosed on smears as "malignant, probably cervical."

TABLE IV. RESULTS OF SMEARS IN NEGATIVE PATIENTS

No. of patients	437
Correct negative smears	430 or 98.4%
False positive smears	7 or 1.6%

There were but five patients with fundal carcinoma. In two of the cases the vaginal smear was reported as negative. There was one case of fibrosarcoma of the uterus, which was correctly reported as positive for uterine malignancy; however in this instance, the type of malignancy was questionable on the basis of the smear, and was finally incorrectly reported as cervical in origin. The abnormal cells noted on the smear were of the elongated spindle variety. The fifty-seven cases of cervical carcinoma were all of the squamous type. A diagnosis of squamous cell carcinoma of the cervix was made by the vaginal smear in forty, or 70.2 per cent of the cases, and missed in seventeen, or 28.8 per cent.

has been our policy, since the completion of this study, that whenever large numbers of cervical or endometrial cells are found which are at all bizarre to ask for repeated smears. Not infrequently much repetition has been rewarded by eventually finding cells suggestive of malignancy. On the other hand, it has been pointed out in the results presented that there have been numerous instances in which the initial smear failed to arouse sufficient suspicion to warrant further investigation. This we regard as the chief danger of the vaginal cytologic method, namely, the false security that a negative report may engender, particularly among those who do not appreciate its limitations.

(3) *The Personal Factor.*—There can be no question that the successful use of the vaginal smear method, even in the hands of competent microscopists, depends largely upon a wide experience in interpreting the cells which may be found on the smears. A large variety of cells which normally may be found in the vagina arise from all parts of the genital tract, and variations due to age, alterations in ovarian activity, functional disturbances, inflammatory reactions, and various benign growths, make it most difficult to evaluate cells regarded as suspicious of malignancy. In analyzing the statistics from different clinics it is quite apparent that the personal factor has been an important one, since some groups have a considerable error in false positives while in others the percentage of false negatives has been greater. Our own practice has been to adopt a rather rigid standard in reporting smears suspicious of malignancy and to indicate other smears containing cells not fully meeting these requirements as "doubtful." Much can be said on both sides of this question. If the diagnostic criteria are made too rigid it is quite possible that positive cases will be overlooked. On the other hand, if smears are reported positive on an insecure basis, unnecessary biopsies or even operations may be performed. Even with our most rigid standards we have had several instances in which biopsy or operation failed to reveal a malignant lesion; yet these have been more than compensated for with several cases in which operation was performed on the basis of a vaginal smear alone and in which carcinoma was found. One such case proved to be a myosarcoma of the tube and in another instance an endometrial carcinoma was discovered in patients not included in this study.

A point not to be overlooked in a study of this kind is the value of the vaginal smear in furnishing information concerning the patient other than the presence of malignant cells. The usefulness of the cytologic smear of determining ovarian function is now well established. Although the cytologic findings in pregnancy are not absolutely characteristic the experienced observer soon learns to detect cells suggesting this possibility in a fairly high percentage of the cases. If in addition one finds evidences of bleeding, plus the presence of decidual cells or even cells from the trophoblast, the diagnosis of threatened abortion is frequently suggested. The vaginal smear picture

Jones and her co-workers⁶ had an error of 11 per cent in false positives and 9 per cent in false negatives in a group of 432 cases, in eighty-two of which a final diagnosis of malignancy was established.

TABLE V. PATIENTS WITH FALSE POSITIVE SMEARS

FINAL DIAGNOSIS	VAGINAL SMEAR
Age 52 years 1. Hyperplastic endometrium Fibromyomata	Squamous cell carcinoma
Age 44 years 2. Functional uterine bleeding	Endometrial carcinoma
Age 22 years 3. Pelvic inflammatory disease	Squamous cell carcinoma
Age 28 years 4. Pelvic inflammatory disease	Squamous cell carcinoma
Age 18 years 5. Pelvic inflammatory disease	Squamous cell carcinoma
Age 24 years 6. Abortion induced?	Endometrial carcinoma
Age 55 years 7. Cervical polyp benign	Squamous cell carcinoma

It will be noted that these statistics, including those reported in the present study, show a considerable degree of variation. This may be attributed to a number of factors inherent in the technique, which may be most conveniently summarized under the following headings:

(1) *Collection of Vaginal Smears.*—There has been considerable discussion as to whether smears should be collected from the posterior fornix of the vagina as originally advocated by Papanicolaou or from the cervix as advocated by Ayre and his associates.⁸ Endocervical and endometrial smears also were suggested by Papanicolaou⁹ as a further diagnostic aid in selected cases. It has been pointed out that the posterior fornix is the natural collecting place for exfoliated cells from every portion of the genital tract and that material collected from this source is most likely to be representative of all portions. On the other hand, if a lesion is visible or accessible, material collected from such a source is most likely to contain a higher proportion of abnormal cells. The percentage of endometrial cells has been claimed to be higher in the cervical secretion than in the vaginal smear. Although the present study was limited to smears taken only from the vagina, other observations which we have made lead us to believe that for routine purposes smears taken from both sources are probably better. We have noted occasional instances in which vaginal smears failed to show abnormal cells although the latter were found in smears prepared from the cervix. Nevertheless, cervical smears alone have not proved generally to be more accurate, in our experience, than those from the vaginal source alone. It has been our recent practice, therefore, to collect both cervical and vaginal smears wherever possible.

(2) *The Number of Smears Examined.*—Unquestionably the larger the number of samplings taken from a patient, the more accurate the results. This factor is an important one and probably explains the remarkable statistics reported by Papanicolaou and Trant,² since they state that many smears were taken from the patients they studied. Unfortunately, this has a certain practical limitation, since if the smear is completely negative and the patient presents no suspicious symptoms or lesions, there would be little reason for repeating smears. It was with this thought in mind that the present study was limited to a single set of smears, and it is our opinion that the high percentage of positive cases missed can be attributed chiefly to this factor. It

OBSERVATIONS ON VAGINAL ABSORPTION OF PENICILLIN*

STUART ABEL, M.D., CHESTER J. FARMER, M.A., AND JEANNE DOUCETTE, B.S.,
CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and Chemistry, Northwestern University Medical School)

DURING a recent investigation of the value of penicillin vaginal suppositories in the treatment of vaginitis, concomitant observations were made relative to blood penicillin levels in the patients treated. Some interesting, if somewhat variable levels were obtained indicating inconsistent vaginal absorption in this group of patients with vaginitis. It seemed propitious to further our knowledge of the rate and degree of absorption of penicillin calcium from the vagina in a control group. Such a control group was organized from among our young single hospital nurses. Subjects in whom blood level studies were conducted were divided into four small groups as follows:

Group I is composed of ten patients from among the cases treated for vaginitis. The accompanying tables include the essential relevant data. One suppository containing 100,000 units of penicillin was inserted vaginally prior to the blood level studies in each patient.

Group II includes five additional patients with vaginitis in whom studies were made subsequent to the insertion of two suppositories (200,000 units). Table II follows.

Group III represents five hospital clinic patients selected at random for similar penicillin blood level studies following vaginal insertion of 200,000 units of penicillin. These five subjects were free of vaginal pathology. The pertinent detail in each case is included in Table III.

And finally, group IV is composed of nineteen of our single hospital nurses. These girls were contacted individually and told in detail of the proposed study. All were normal young menstruating women free of gynecologic pathology. Four studies were made in each volunteer at different stages during a menstrual cycle beginning at the completion of a period and ending just prior to the onset of the subsequent period. The blood levels in each instance again were determined following the vaginal insertion of two penicillin suppositories (200,000 units). During the ensuing four hours while the study was in progress, the girls were instructed to remain quietly in bed. Again the accompanying table includes the pertinent data.

The average blood levels for groups I, II and III are represented in the following graph. As seen in Table IV, the few levels obtained in group IV were so low as to be unassayable by the method used. Graphic representation of the results in group IV is not possible.

*Vaginal suppositories were generously supplied by the Schenley Corporation, New York.

TABLE I. (100,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	VAGINAL EXAMINATION	VAGINAL SECRETIONS	VAGINAL CULTURE	BLOOD LEVELS						DATE
						1/2 IIR.	1 IIR.	2 IIR.	3 IIR.			
A. K.	56	Postmenopausal LAP 1939	Senile vaginal mucosa with vaginitis	Not reported	Not reported	1.0	1.0	.50	.25			7/ 5/46
M. D.	48	Postmenopausal LAP 1930	Senile vaginal mucosa with vaginitis	Few WBC Few bacteria	Diphtheroids; <i>B. Coli</i>	1.0	.50	0.0	0.0			8/23/46
E. M.	41	LAP March, 1944	Recent vaginal plastic operation; marked vaginitis	Many WBC Rare RBC Many bacteria	<i>Staph. albus</i> , non-hemolytic Alpha hemolytic streptococcus	0	0	0	0			7/15/46
R. K.	30	Cycle 28/5 LAP 7/10/46	Endocervicitis; vaginitis with much leucorrhea	Moderate WBC Moderate bacteria Occ. RBC	Nonhemolytic <i>Staph. albus</i>	.125	.125	.06	.03			7/15/46
E. L.	59	Postmenopausal LAP 1937	Senile vaginal mucosa with severe vaginitis and profuse leucorrhea	Many bacteria Many WBC	Nonhemolytic streptococcus	0.0	.06	.05	.06			7/10/46
M. K.	26	Cycle 28/4 LAP 6/28/46	Marked vaginitis	Many WBC Mod. bacteria Occ. tricho.	Nonhemolytic <i>Staph. albus</i> Hemolytic <i>Staph. albus</i> Nonhemolytic streptococcus	.03	.03	0	0			7/15/46
V. P.	28	Cycle 28-32/5 LAP 6/5/46	Endocervicitis; vaginitis with much leucorrhea	Many WBC Many bacteria	Diphtheroids	.12	.50	.50	.50			8/12/46
M. D.	25	Cycle 28/5 LAP 7/7/46	Severe vaginitis	Many WBC Many bacteria	Diphtheroids	.125	1.0	.25	.03			7/22/46
E. L.	53	Postmenopausal LAP 1941	Senile vaginal mucosa with vaginitis	Many WBC Many RBC Many bacteria	Nonhemolytic <i>Staph. albus</i> ; <i>B. Coli</i>	4.0	1.0	.25	.06			7/ 3/46
A. T.	23	Cycle 28/6 LAP 9/19/46	Marked vaginitis with leucorrhea; typical trichomonous	Many WBC Many bacteria Many tricho.	Moderate gamma streptococcus and diphtheroids	.25	.50	.125	.06			7/15/46

TABLE II. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	VAGINAL EXAMINATION	VAGINAL SECRETIONS	VAGINAL CULTURE	BLOOD LEVELS				DATE
						1/2 HR.	1 HR.	2 HR.	3 HR.	
C. W.	34	Cycle 28/5 LMP 7/22/46	Severe vaginitis; typical tricho.	Many WBC Many bacteria Many tricho.	Diphtheroids Micrococci Alpha streptococcus	0.0	0.0	.125	0.0	7/30/46
C. B.	59	Postmenopausal LMP 1941	Senile vaginal mucosa with vaginitis	Many WBC Many bacteria	Diphtheroids Alpha streptococcus	0.0	0.0	0.0	0.0	7/30/47
J. F.	23	Cycle 21/8 LMP 6/8/46	Endocervicitis and vaginitis	Many WBC Many bacteria	Diphtheroids <i>Staph. albus</i>	0.0	.25	1.0	2.0	10/23/47
E. L.	59	Postmenopausal LMP 1937	Senile vaginal mucosa with vaginitis and severe leucorrhea	Many WBC Many bacteria	Nonhemolytic streptococcus	2.0	1.0	.125	0.0	11/15/46
L. C.	31	Abd. complete hysterectomy in April, 1946; both ovaries left in	Vaginitis	Many WBC Many bacteria	Alpha streptococcus <i>B. Subtilis</i>	0.0	.25	.25	.25	8/13/46

TABLE III. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	GYNECOLOGIC PATHOLOGY	BLOOD LEVELS			
				1/2 HR.	1 HR.	2 HR.	3 HR.
B. V.	39	LMP just prior to test—periods irregular	Had vaginal plastic No pathology now Vagina clean (intermenstrual spotting)	0.0	0.0	0.0	0.0
S. R.	46	Cycle 21-28/10 LMP 11/9 Test 11/19	No pathology (menorrhagia) Vagina clean	0.0	0.0	0.0	0.0
N. D.	51	LMP 23 years ago following abdominal section	Large cysto- and rectocele Cervix and part of corpus seemed present (no vaginal pathology)	1.0	2.0	1.0	0.50
M. R.	60	LMP 19 years ago	No gynecologic pathology Vagina clean (Vaginal spotting?)	0.0	0.50	0.50	0.50
H. L.	43	Cycle 28/5 LMP 3 weeks prior to test	Cystocele and rectocele Vagina clean	0.0	0.25	1.0	0.25

The method of assay employed for this work was the Fleming-Wright slide cell technique as described by Heilman and Herrill¹ with the omission of dilution transfer to the slides. Defibrinated rabbit blood containing a beta hemolytic streptococcus sensitive to penicillin (culture C203) was added to the serial dilutions of the serums and incubated overnight. On the following day the assay was observed for presence or absence of hemolysis. The last tube of the serial dilution containing blood serum showing no hemolysis was taken as the end point and its contents of penicillin was considered identical to that of a standard prepared similarly containing a known amount of penicillin.

Discussion

From the results obtained one is impressed with the extreme variability of blood penicillin levels following insertion of penicillin vaginal suppositories. It is interesting to note the marked differences in levels obtained among individual patients within the same group. The lack of appreciable levels in the well-controlled group of nurses is particularly striking. A short comment relative to the few recent articles dealing with vaginal absorption of penicillin seems appropriate before attempting to evaluate our own results.

Lovelady, Randall, and Hosfeld² reported blood penicillin levels in thirty-six postpartum patients following the insertion of vaginal suppositories. These patients were confined to bed. No mention is made of the elapsed time since the patients were delivered. The thirty-six patients were divided into three groups of one dozen each. In the first group one suppository was used (100,000 units penicillin), in the second group two suppositories were used, and in the third group three suppositories were used. Levels were determined at three and five hours by the slide-cell technique of Heilman. In group one, five patients showed a low blood level after three hours and seven did not. There were no levels at five hours. Six of the patients in group II showed a somewhat higher level at three hours and in two of these there was still an appreciable level at five hours. In group III all but three of the twelve patients showed levels at three hours,

one as high as 0.5 units per c.c. serum. Appreciable levels were maintained in seven of these patients for 5 hours. From their results the Mayo group advocated the use of the suppositories as a routine measure in the preparation of patients for delivery and perhaps in preparation for Cesarean section or hysterectomy. There is no evidence that absorption from the postpartum vagina necessarily indicates absorption in other conditions.

Rock, Barker, and Bacon³ reported from Harvard Medical School on their experiences with the vaginal absorption of penicillin. They concluded that except during the last two months of pregnancy, penicillin is easily absorbed from cocoa butter suppositories in the vagina, giving therapeutic blood levels for from four to six hours. These conclusions were based on nine nonpregnant patients with vaginitis or cervicitis and four patients who were awaiting delivery. Seven recently delivered postpartum patients comprising a third group also showed good blood levels.

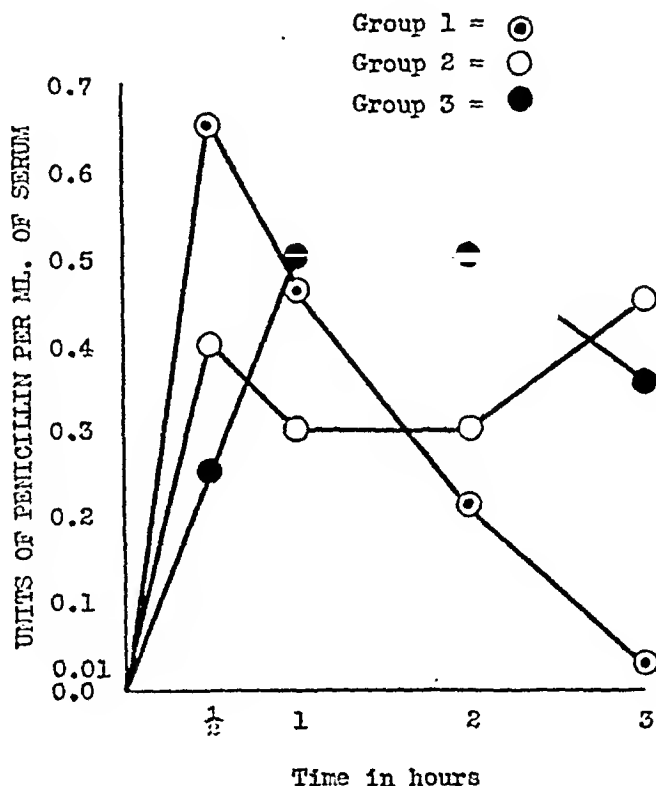


Fig. 1.

Goldberger, Walter, and Lapid⁴ concluded that penicillin in the form of suppositories is readily absorbed through the vagina and that therapeutic levels are easily attained and maintained for at least three hours. These workers used 500,000 units of penicillin. Their average blood penicillin levels at the end of one-half, one, two, and three hours were 0.38 units, 1.35 units, 0.96 units, and 0.38 units respectively. Studies were conducted in ten patients, seven of whom were normal menstruating women. Two were postmenopausal and one was amenorrheic with virilism. All were free of vaginal pathology. Vaginal pH studies were made prior and subsequent to the tests. On studying the table of results, no correlation of the age, menstrual cycle, or the vaginal pH with the levels obtained is apparent. The authors conclude that the vaginal route may be the method of choice for the administration of penicillin in the adult female.

TABLE IV. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	DAY OF CYCLE	BLOOD LEVELS			
				$\frac{1}{2}$ HR.	1 HR.	2 HR.	3 HR.
A. A.	22	Cycle 28/7 LMP 1/1/47	1/ 6/47	0	0	0	0
			1/13/47	0	0	0	0
			1/20/47	0	0	0	0
			1/23/47	0	0	0	IC
A. H.	26	Cycle 28-30/4 LMP 1/2/47	1/ 6/47	0	0	0	0
			1/14/47	0	0	0	0
			1/21/47	0	0	0	0
			1/29/47	0	0	0	0
M. K.	26	Cycle 30/7-8 LMP 12/29/46	1/ 6/47	0	0	0	0
			1/13/47	0	0	0	0
			1/20/47	0	0	0	0
			1/27/47	0	0	0	0
D. O.	24	Cycle 28/4 LMP 1/3/47	1/ 7/47	0	0	0	0
			1/15/47	0	0	0	0
			1/23/47	IC	0	0	0
C. U.	25	Cycle 21/5 LMP 1/5/47	1/ 9/47	0	0	0	0
			1/14/47	0	0	0	0
			1/21/47	0	0	IC	0
			1/25/47	0	0	0	0
S. H.	27	Cycle 22/7 LMP 1/7/47	1/13/47	0	0	0	0
			1/20/47	0	0	0	0
			1/27/47	0	0	0	0
			2/ 2/47	0	0	0	0
W. F.	24	Cycle 30/5 LMP 1/7/47	1/11/47	0	0	0	0
			1/20/47	0	0	0	0
			1/28/47	IC	IC	0	0
			2/ 6/47	0	0	0	0
A. G.	26	Cycle 28/4 LMP 1/29/47	2/ 3/47	0	0	0	0
			2/10/47	0	0	0	0
			2/17/47	0	0	0	0
			2/24/47	0	0	0	0
A. H.	25	Cycle 30/5 LMP 1/5/47	1/ 9/47	0	0	0	0
			1/17/47	0	0	0	0
			1/27/47	0	0	IC	0
			2/ 3/47	0	0	0	0
R. W.	23	Cycle 28/5 LMP 1/13/47	1/18/47	0	0	0	0
			1/27/47	0	0	0	0
			2/ 2/47	0	0	0	IC
			2/ 8/47	0	0	0	0
C. C.	22	Cycle 28/5 LMP 1/12/47	1/18/47	0	0	0	0
			1/25/47	0	0	0	0
			2/ 1/47	0	0	0	0
			2/ 8/47	0	IC	IC	0
J. B.	25	Cycle 28/4-5 LMP 1/15/47	1/20/47	0	0	0	0
			1/28/47	0	0	0	0
			2/ 5/47	0	0	0	0
			2/13/47	0	0	0	0
C. C.	23	Cycle 25/5 LMP 1/10/47	1/14/47	0	0	0	0
			1/21/47	0	0	0	0
			1/28/47	0	IC	0	0
			2/ 4/47	0	0	0	0
E. A.	26	Cycle 28/4-5 LMP 1/9/47	1/14/47	0	0	0	0
			1/21/47	0	0	0	0
			1/28/47	0	0	0	0
			2/ 6/47	0	0	0	0

TABLE IV—CONT'D

NAME	AGE	MENSTRUAL HISTORY	DAY OF CYCLE	BLOOD LEVELS			
				$\frac{1}{2}$ HR.	1 HR.	2 HR.	3 HR.
R. B.	29	Cycle 28/5 LMP 1/16/47	1/21/47	0	0	0	0
			1/29/47	0	0	0	0
			2/ 5/47	0	0	0	0
			2/12/47	0	0	0	0
C. G.	24	Cycle 28/5 LMP 1/13/47	1/ 7/47	0	0	0	0
			1/25/47	0	0	0	0
			2/ 1/48	0	0	IC	0
			2/ 8/48	0	IC	0	0
W. P.	22	Cycle 25/4 LMP 1/22/47	1/25/47	0	0	0	0
			2/ 1/47	0	0	0	0
			2/ 8/47	0	0	0	0
			2/15/47	0	0	0	0
A. D.	34	Cycle 28/4-5 LMP 1/15/47	1/20/47	0	0	0	0
			1/28/47	0	0	0	0
			2/ 4/47	0	0	0	0
			2/11/47	0	0	0	0
J. K.	23	Cycle 28-30/6 LMP 1/20/47	1/24/47	0	0	0	0
			2/ 3/47	0	0	0	0
			2/10/47	0	0	0	0
			2/17/47	0	0	0	0

IC—incomplete hemolysis which is interpreted to represent amounts so small that they were unassayable.

The most recent report is a paper by Seludnak and Hesseltine⁵ of the University of Chicago. Their paper on "The Absorption of Penicillin from the Human Vagina" was read by title at a recent meeting of the Illinois section of the Society of Experimental Biology and Medicine. Although this paper is not available at the time of this writing, one of the authors has informed us through personal communication that vaginal absorption of penicillin as determined by their studies has been inconstant and unpredictable. This has certainly been our experience.

From the literature and from our own results it appears that there is some degree of vaginal absorption of penicillin under certain circumstances. However, the degree of absorption is extremely inconstant and unpredictable. A possible relationship of the vaginal pH and the degree of absorption occurred to us but Goldberger and his workers have not demonstrated any correlation. It seems feasible that the inflamed vaginal mucosa with the accompanying hyperemia incident to vaginitis might be conducive to a degree of absorption different from that of the normal vaginal mucosa in a healthy young patient. In the group of nineteen nurses, all subjects were at bed rest and loss of penicillin from the vagina was kept at a minimum. Tests were conducted by the same method and personnel as applied to our other three groups. The consistent lack of appreciable blood levels of penicillin in this group must be significant.

Goldberger's conclusion that vaginal administration of penicillin may be the method of choice in adult women seems unjustified in the light of our studies, if the production of therapeutic blood levels is the desired result. It

appears that such levels are not dependable following vaginal absorption of penicillin and that intramuscular administration is more feasible.

It is of importance to note that two of the nineteen nurses developed urticaria during the study and two of the patients with vaginitis and leucorrhea developed pruritus only after they had been on treatment some time and after the vaginitis and leucorrhea were much improved. Whether or not the pruritus was caused by the penicillin is problematical.

From our own experiences and those of others reporting recently, vaginal penicillin suppositories are of real value in the treatment of vaginitis. Such value probably stems from the local concentration rather than from the blood level obtained by absorption. The real value of vaginal penicillin suppositories is in the treatment of vaginitis, and the blood levels achieved during such therapy are incidental and of doubtful importance.

Conclusions

1. Penicillin, when administered in cocoa butter suppositories, is absorbed from the vagina under certain conditions.

2. The degree of absorption and the resulting blood penicillin level are subject to great variation and are difficult to predict in any given case. Apparently there is less absorption of penicillin from the normal vaginal mucosa than from the inflamed mucous membrane in a patient with vaginitis.

3. Because of the incidence of side reactions and, because of the unpredictable blood levels obtained subsequent to the use of penicillin vaginal suppositories, it does not seem rational to advocate this route of administration in preference to intramuscular injection or oral therapy when the desired result is the production and maintenance of a therapeutic blood penicillin level.

4. The real value of penicillin vaginal suppositories is in the treatment of vaginitis where the local concentration of penicillin is of prime importance and the production of blood levels is only a matter of secondary interest.

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720 NORTH MICHIGAN AVENUE.

THE PERMEABILITY OF THE HUMAN PLACENTA TO SODIUM IN NORMAL AND ABNORMAL PREGNANCIES AND THE SUPPLY OF SODIUM TO THE HUMAN FETUS AS DETERMINED WITH RADIOACTIVE SODIUM

L. B. FLEXNER, M.D., D. B. COWIE, PH.D., L. M. HELLMAN, M.D.,
W. S. WILDE, PH.D., AND G. J. VOSBURGH, M.D., BALTIMORE, MD.

*(From the Department of Embryology, Carnegie Institution of Washington, Baltimore,
Department of Terrestrial Magnetism, Carnegie Institution of Washington, Washington,
and the Department of Obstetrics, Johns Hopkins University and Hospital)*

TO OBTAIN comprehensive information on the permeability of the placenta, one should be in a position, ideally, to measure its permeability to many and diverse test substances. These substances should be closely related chemically and physically to those constituents of the maternal plasma which are normally transferred across the placenta from mother to fetus. The availability of radioactive and stable isotopes, together with exquisitely sensitive and reliable methods for their quantitative measurement, has furnished a method which satisfies this criterion. Because of the chemical identity of these isotopes with their naturally occurring counterparts in the body, we are assured that their biological behavior is normal when the precaution is taken of using radioactive substances in amounts substantially less than that known to produce radiation effects. A molecule may be identified or "marked" with an isotope (e.g., in "heavy water," hydrogen of atomic weight 2 replaces its isotope, hydrogen of mass 1, found in ordinary water) and the molecule subsequently traced by detecting the isotope. Or the isotope may be studied as an ion (e.g., Na^{24} which is radioactive and which is detected by one of several instruments used for measuring radioactivity).

The investigations to be reported here had as their objective the measurement of the permeability of the human placenta to sodium, primarily in normal cases, and, as occasion permitted, in the presence of disease. The observations have been made in twenty-seven women in whom pregnancy was terminated by abdominal hysterotomy before the period of viability or by cesarean section or pelvic delivery at or near term. Ten of these cases were presented in a preliminary report.¹ We entered upon this program with a background of studies on the placentas of animals representing each of Grosser's four morphological types²; we are able, consequently, to consider the results on man from the viewpoint of comparative physiology, and to relate them to the results obtained from other members of the hemochorial group. As in the animals studied, we shall also be interested, at various stages of pregnancy, in the amount of sodium supplied to the human fetus as this is related to the fetal need for sodium during growth.

Rationale and Methods

When a radioactive isotope is used in biological research it is mixed with a preponderant quantity of its naturally occurring, nonradioactive isotope; the radioactive substance is employed to tag or label the naturally occurring substance so that the latter may be distinguished from that already present in the body. Thus when radioactive sodium (Na^{24} , i.e., Na with an atomic weight of 24) is used to study the behavior of sodium (Na^{23}) intrinsic to the body, the Na^{24} is present in the sample in an infinitesimally small amount as the chloride together with a weighable amount of ordinary NaCl. The mixture of the two isotopes is referred to as tagged or labeled sodium, and will be designated by the symbol Na^* . In practice, a sample of tagged sodium is weighed and the radioactivity measured in terms of the radiation or counts emitted per second; if the radioactivity of any part of the sample is subsequently known, it is then possible to calculate the corresponding weight of the tagged sodium which is present. We shall present our data in terms of tagged sodium; it will be evident that this refers to sodium (Na^{24} plus Na^{23}) introduced into the body and is not to be confused with the sodium intrinsic to the body. The quantities of tagged sodium used in our experiments were kept as small as were compatible with precise measurements of their radioactivity and were so minute in comparison to the normal sodium content of the body that they are properly called tracer quantities (see Table I).

The fundamental assumption in the use of a radioactive isotope to measure placental permeability is that the radioactive substance crosses the membrane precisely as does its naturally occurring isotope, and therefore, the two isotopes cross the placenta in the same proportion as is found in the fluid bathing it. In the case of the placenta this means that:

$$\frac{\text{Na}_{\text{mp}}}{\text{Na}^*_{\text{mp}}} = \frac{\text{Na}_f}{\text{Na}^*_f} \quad (1)$$

where Na_{mp} refers to the concentration of normally occurring sodium in the maternal plasma, Na^*_{mp} to the concentration of tagged sodium in the maternal plasma; and Na_f and Na^*_f are the quantities of the corresponding substances transferred to the fetus during the time of an experiment.

Our experimental data have as a first aim the evaluation of Na_f . This quantity divided by the weight of the placenta will be taken as a measure of placental permeability to sodium. Na_f can be calculated from equation (1) if the other three quantities are known. The concentration of sodium in human plasma, Na_{mp} , has been frequently determined, and has an average value of 3.3 mg. per 100 c.c. of plasma.² The evaluation of Na^*_{mp} is less direct. After injection of a solution of Na^*Cl into a maternal vein the concentration of Na^* in the plasma rapidly diminishes due to its passage into the extracellular fluid of the mother. Since the amount of labeled sodium transferred to the fetus is directly proportional to its concentration in the maternal plasma, only the average concentration in the maternal plasma during the period of transfer is suitable for substitution in the equation. Our first series of experiments, therefore, was designed to measure the rate of disappearance of labeled sodium after its intravenous injection; and from these data the average plasma concentration was obtained. The measure of the quantity of labeled sodium transferred to the fetus (Na^*_f), moreover, is valid for substitution in the equation only if none returns from fetus to mother during the period of observation. It is reasonable to assume that early after introduction of the tagged sodium into the maternal circulation, its concentration in fetal plasma remains so low compared to that of maternal plasma that only a negligible quantity returns from fetus to mother. This condition was taken to be satisfied in the guinea pig⁴ when the concentration of the tagged

sodium in the fetus (referred to a unit concentration of tagged sodium in the maternal plasma) increased linearly with time. The period of linear exchange in the guinea pig lasts for from two to three hours after injection; the rate of accumulation in the fetus then decreases until equilibrium is reached at about eight hours. Because of experimental limitations we have not been able to determine the period of linear acquisition by the human fetus. To be as certain as possible about procedure, however, delivery of the fetuses has usually been made approximately thirty minutes after injection of the radioactive material. This procedure gave concentrations of labeled sodium in the fetus as related to unit concentration in the maternal plasma well below the ratio for linearity in the guinea pig.

The umbilical cord was clamped as soon as possible, usually within a minute, after incision of the uterus was begun. Immediately thereafter a sample of maternal blood was taken. The fetus and placenta were weighed, the latter being freed of its membranes, cord, and superficial blood. Nonviable fetuses were ashed as previously described⁴; blood samples were secured from viable fetuses one to three hours after delivery. This time interval was chosen to permit equilibration of plasma sodium with extracellular sodium. The radioactivity of the samples of maternal plasma, fetal ash, and of the fetal plasma was then measured and the quantity of tagged sodium present in these samples calculated from the radioactivity. The total quantity of tagged sodium in a viable fetus was calculated from the concentration found in the plasma and from the known volume of the extracellular space which has been found to average 43.5 per cent of the body weight.⁵ The average value for the concentration of tagged sodium in maternal plasma was obtained as will be described below in the presentation of the disappearance curve of tagged sodium from plasma.

The labeled sodium was prepared in the 60-inch cyclotron of the Department of Terrestrial Magnetism, Carnegie Institution of Washington, by deuteron bombardment of metallic sodium. After bombardment, the sodium was dissolved in ethyl alcohol, and Na^{24}Cl then precipitated with concentrated HCl . Finally an aqueous solution of Na^{24}Cl was made using distilled water. Appropriate precautions were taken with respect to tonicity, neutrality and sterility of the solution. The amount of tagged sodium injected into an individual averaged about 30 mg. with an activity of 0.3 millieurie. The radioactivity of the samples was measured by a temperature controlled, pressure ionization chamber connected to a string electrometer⁴; these measurements were corrected for self-absorption of radiation by the sample and for the background of the instrument.

Results

The disappearance curve for Na^{24} in plasma after its intravenous injection.—As has been pointed out, the calculation of the placental transfer rate for sodium depends upon an accurate estimation of the average maternal plasma concentration of Na^{24} present during the period of transfer under observation. This entails the description of the change in concentration of Na^{24} in maternal plasma from the time of its intravenous injection until the time of delivery of the fetus. Multiple sampling of maternal blood at the time of the transfer studies was avoided by establishing a time-concentration curve in advance (Fig. 1). This was accomplished by injecting a known quantity of Na^{24} into each of three normal, pregnant women. The curve was standardized so that the average concentration for a given pregnant subject could be determined by measurement of the Na^{24} concentration of a single plasma sample taken at a known time. This

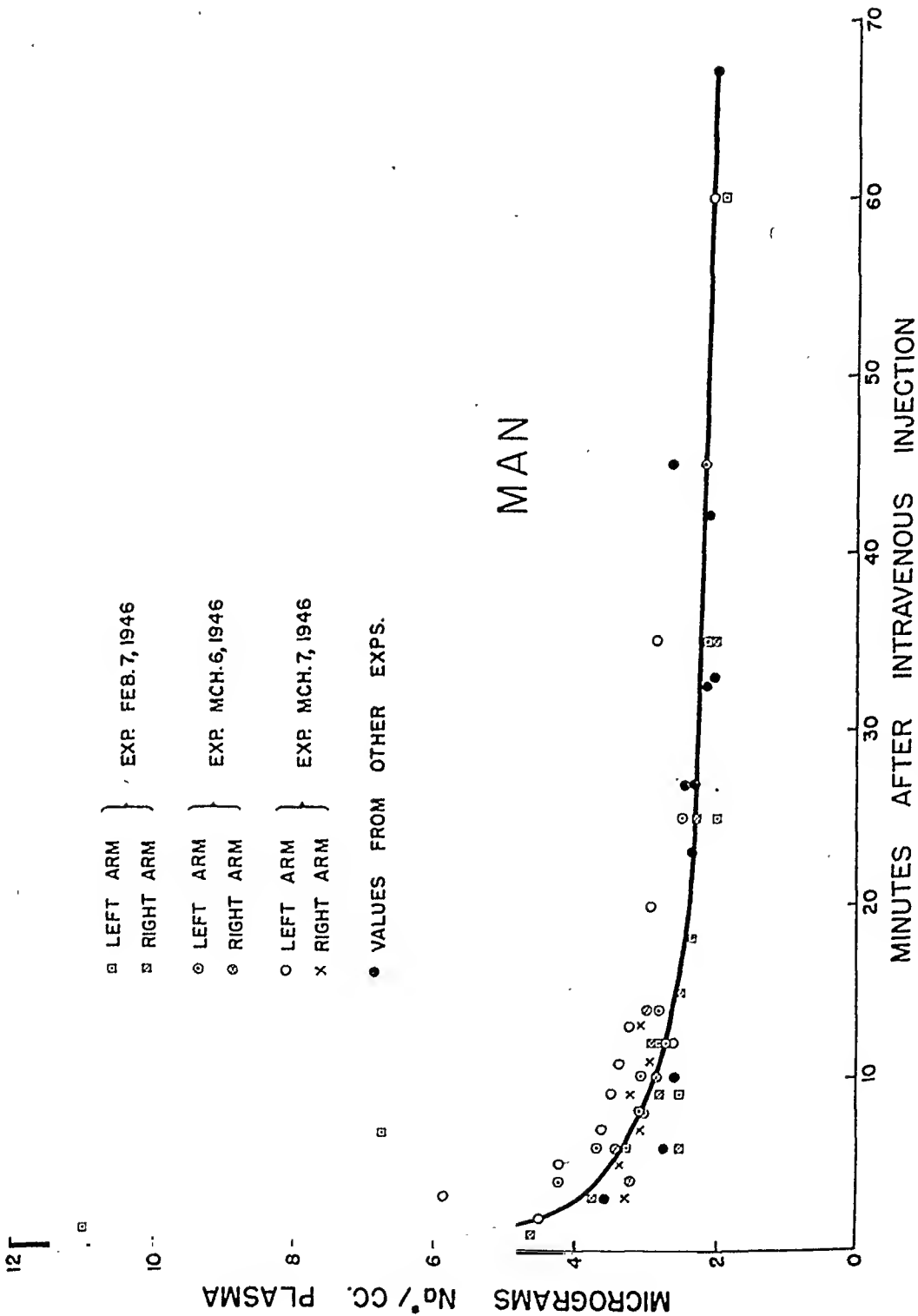


FIG. 1.—Change in concentration of Na⁺ in the plasma with respect to time. The points were adjusted to a standard basis by multiplying them all by a factor which brought the initial concentration to 12 micrograms per c.c. of plasma, as explained in the text.

was done as follows: For each of the three individuals studied we calculated the plasma concentration of Na^* which could have been present immediately after injection if the injected Na^* had been distributed uniformly in the plasma. A standard plasma volume of 45 c.c. per kilogram body weight was assumed. This initial concentration (which varied among the three subjects but averaged about 12 micrograms Na^* per c.c. of plasma) in each woman was multiplied by whatever factor was necessary to convert it to a standard concentration of 12 micrograms Na^* per cubic centimeter of plasma. Subsequent measurements of plasma concentration in each of the three cases were then multiplied by the same factor. Since the standard plasma volume which has been used as a constant, this treatment is equivalent to relating all concentrations to a constant quantity of Na^* per unit body weight. The average concentration of Na^* in the maternal plasma for a period of thirty minutes after injection was obtained from the standard curve of figure 1 as follows: The area under the curve from zero time to thirty minutes was measured with a planimeter. This area was then divided by the time interval, thirty minutes, to obtain the average altitude, or average concentration. The ratio of this concentration to that found at thirty minutes is the factor, 1.35, by which the concentration of Na^* at thirty minutes in a subject must be multiplied to give the average concentration for that subject. Average maternal values calculated in this way are given in the last column of Table I.

As shown in Fig. 1, samples of blood were taken simultaneously from veins of the right and left arms. This provided a measure of mixing time and it was assumed that mixing was essentially complete when the amount of Na^* in the two samples was about equal. In one subject, the mixing time estimated in this way amounted to about eight minutes; in the second, to twelve minutes; and in the third, to thirteen minutes. The average concentration of Na^* in the maternal plasma will of course be affected by the mixing time. We believe that for our purpose the average concentration in the maternal blood of the placenta differs in no important way from that of the peripheral blood as we have established it.

The normal placental transfer rate for sodium at different gestational ages.—The amount of sodium transferred to a fetus during an experiment was calculated from equation 1. Values for Na^*_{f} and Na^*_{mp} , the latter averaged for the observed period of transfer, are given in Table I. Na_{mp} was taken to equal 3.3 mg. per c.c. The value of Na_{f} derived from these data was finally converted to milligrams of sodium transferred across one gram of placenta in one hour. The results are presented in Fig. 2.

The curve of Fig. 2 has been drawn to fit observations made on individuals in which there was no reason to suspect abnormality of placental function. Sixteen normal cases in this series were distributed among individuals who were delivered abdominally because of previous section, mental disease, chorea, tuberculosis, myoma of the uterus, pyelitis, or carcinoma of the abdomen. In addition there are two cases which have been observed during normal labor and vaginal delivery. Six of these cases fell within the ninth to seventeenth week of pregnancy; ten were between the thirty-sixth week and term; only three came between the seventeenth and the thirty-sixth week because of the rarity of interruption of pregnancy during this period.

TABLE I. VALUES FROM WHICH THE DATA OF FIG. 2 AND TABLE II HAVE BEEN DERIVED*

HISTORY NUMBER	INDICATION FOR OPERATION	DELIVERY TIME (MINUTES)	FETAL WEIGHT (GM.)	GESTATION AGE (WEEKS)	PLACENTAL WEIGHT (GM.)	NR* IN TOTAL FETUS (MICROGRAM)	NR*/C.C. OF MATERNAL PLASMA	
							FOUND (MICROGRAM)	AVERAGE (MICROGRAM)
103003	Previous section	33	2700	38	370	700	1.49	1.94
247063	Psychiatric	27	402	16	126	39.0	0.97	1.31
231656	Psychiatric	30	36	10	63	9.5	1.29	1.74
249863	Psychiatric	32	545	20	156	167	1.42	1.84
260095	Previous section	27	2180	37	214	668	4.43	5.98
113669	Twin pregnancy	28	2030	40	205	264	4.43	5.98
128414	Previous section	28	3040	term	490	1230	2.67	3.60
376433	Pelvic delivery	55	3340	37	505	1120	1.34	1.60
388120	Previous section	33	3430	37	516	760	1.69	2.20
311276	Chorea	29	92	14	92	19.0	2.40	3.23
254037	Previous section	32	2100	34	370	835	1.79	2.34
386115	Pulmonary tbc.	30	4	9.5	19	0.61	0.88	1.18
136080	Pelvic delivery	30	3680	40	490	1240	1.60	2.16
398157	Myoma uterus	32	2790	36	490	1560	2.35	3.06
396381	Contracted pelvis	31	2630	36	375	1080	1.92	2.59
406823	Chr. pyelitis	46	1500	31	243	1120	3.00	3.80
408367	Ca. abdomen	30	152	17	97	67.0	2.86	3.86
257328	Contracted pelvis	30	2490	40	335	1190	3.86	5.22
240415	Epilepsy	35	19	12	34	10.5	3.58	4.65
165446	Chr. nephritis	31	14	12	34	30.4	4.33	5.84
250383	Hypertension	29	129	16	100	74.3	2.97	4.00
259938	Hypertension	27	614	24	168	49.0	0.45	0.61
389368	Hypertension	28	361	20	140	138	2.97	4.00
247202	Pre-eclampsia	31	2780	37.5	455	1190	2.24	3.02
250393	Pre-eclampsia	28	354	18	100	7.3	0.22	0.30
317603	Cardiac disease	31	1480	31	220	524	4.70	6.10
376618	Cardiac disease	29	247	18.5	121	278	2.00	5.20
		34	201	18	107	64.8	1.72	2.25

The average concentration of Na in the maternal plasma for the duration of the experiment has been calculated as explained in the text. Delivery time refers to the interval between i.v. injection of Na* and clamping of the umbilical cord.

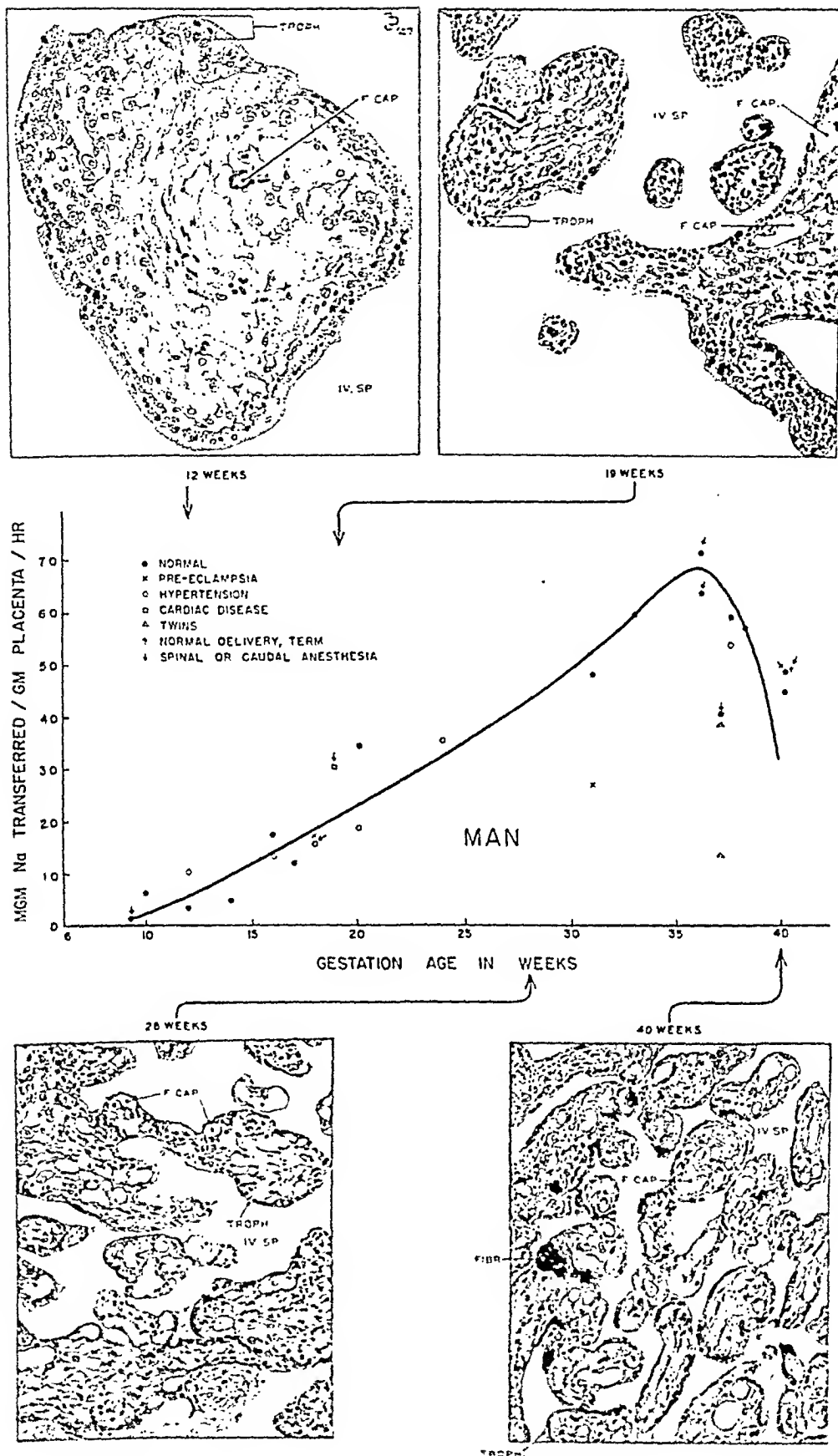


Fig. 2.—Variation of the rate of transfer of sodium with respect to gestation age. The points have been derived from the data of Table 1. The camera lucida drawings ($\times 155$) are from sections of normal human placentas at the indicated gestational ages and illustrate the histological changes which can be correlated with the change in permeability. Note, as the placenta ages, decrease in thickness of trophoblast (Troph.), increase in surface of villi exposed to intervillous space (IV. Sp.), and increase in number of fetal capillaries (F. Cap.). Fibr., fibrin.

Several conclusions of major interest to us are to be drawn from the results. The first is that the apparent permeability of the human placenta to sodium increases about 70 times from the ninth to the thirty-sixth week of gestation. The second is that from the thirty-sixth week to term there was in all but one case a rapid decrease in permeability; this decrease was most marked in a single case of twins. The third is that in the two cases where transfer was observed during normal labor for the half hour or hour preceding delivery, there was no decrease in transfer rate. And finally there was no evident difference between the transfer rates when spinal or caudal anesthesia was used and when general anesthesia was obtained with sodium pentothal or gas-oxygen-ether.

The effect of chronic hypertension, cardiac disease and pre-eclampsia on the placental transfer rate.—Five patients with chronic hypertension were studied, one complicated by chronic nephritis. Three of these were between the twelfth and twentieth weeks of pregnancy, one at the twenty-fourth week and the last near term. They varied in severity from mild degrees of hypertension with blood pressures of 140 to 150 over 90, to severe cases with retinal arteriosclerosis and hemorrhages and blood pressures of 180 over 110 or 120. As shown in Fig. 2, there was no evidence of abnormality of placental transfer in any of these cases.

Measurements were made on two patients with cardiac disease, both in the nineteenth week of pregnancy. In one there was complete heart block, diminished cardiac reserve and considerable vasomotor instability; in the other, rheumatic heart disease with mitral stenosis, a bundle branch block and moderate diminution in cardiac reserve. Both of these individuals had normal placental transfer rates.

Finally, observations were made on two cases of pre-eclampsia. One at a gestational age of eighteen weeks had severe hypertension and albuminuria with retinal hemorrhage and partial retinal detachment. The transfer rate in this patient was normal. The other woman, in the thirty-first week of pregnancy, had edema in addition to severe hypertension and albuminuria. The transfer rate in this case was reduced about 50 per cent; this is the single instance in our series where there has been a definite alteration.

Fetal need for sodium relative to its supply across the placenta.—The ratio of the quantity of a substance supplied to the fetus from the maternal plasma to the amount of that substance retained by the fetus in its growth has been called the safety factor for that substance.⁴ The quantity of sodium transferred to the fetus across the placenta per hour is calculated from equation (1) as explained above. The amount of sodium retained by the fetus in an hour's growth is equal to the fetal weight multiplied by the hourly per cent weight increase of the fetus multiplied by the total sodium in a unit weight of fetal tissue. The safety factor has been calculated for four fetal ages and is given in Table II. The value of the safety factor varies from 160 at a fetal age of twelve weeks to the remarkably high value of 1130 at forty weeks. This means that of 1,130 parts of sodium delivered to the fetal circulation at forty weeks only one part is retained by the fetus in its growth, and 1,129 parts are returned to the maternal circulation.

TABLE II. FETAL NEED FOR SODIUM RELATIVE TO SODIUM SUPPLIED ACROSS PLACENTA AT VARIOUS GESTATION AGES*

FETAL AGE (WEEKS)	FETAL WEIGHT (GM.)	TOTAL Na OF FETUS (MG.)	DAILY WEIGHT INCREASE (PER CENT)	TOTAL Na RETAINED DAILY IN GROWTH OF FETUS (MG.)	Na SUPPLIED TO FETUS PER DAY (MG.)	SAFETY FACTOR
12	18.2	21	11.5	2.4	390	160
20	259	620	2.9	18	5600	310
30	960	2250	1.5	34	20600	610
40	2915	5100	1.1	56	63000	1130

*The daily per cent weight increase has been calculated from the data of Streeter,⁶ and the sodium content of the fetuses is that found by Job and Swanson.⁷

Discussion

As stated in the introduction of this paper, we have been primarily concerned with the following problems: (1) measurement of the permeability of the normal human placenta to sodium from early in gestation to term; (2) comparison of the permeability of the human placenta with that of other placentas of the hemochorial group; (3) measurement of the effects of disease on placental permeability and (4) evaluation of the supply of sodium to the fetus as this is related to the requirement for sodium during fetal growth.

The human placenta, as is true for all the placental types which have been studied with the tracer technique,⁸ undergoes a very considerable increase in permeability to sodium as gestation proceeds. The peak in transfer rate per unit weight of placenta occurs at about the thirty-sixth week when it is approximately 70 times as great as at the ninth week, the earliest case in our series. This peak is followed by a rapid decline in permeability to term. These changes can be correlated with morphological changes which occur in the placenta during the process of aging. The illustrations of Fig. 2 are typical of placentas of twelve, nineteen, twenty-eight and forty weeks of pregnancy. They are all made at the same magnification ($\times 155$) and show clearly some of the important alterations in this organ as gestation progresses. At twelve weeks, the villi are large, relatively few in number and covered with a double layer of cells, the outer, syncytial and the inner, cellular. At nineteen weeks there is an increase in the number of villi, a decrease in their size and Langhans' layer has almost completely disappeared. The increase in total cross sectional area of the villi, together with thinning of their walls, continues through the twenty-eighth week to term. Higher magnification reveals in addition, as pregnancy proceeds, an increase in number of fetal capillaries within the stroma of the villus together with a decrease in the thickness of the capillary walls. The terminal sharp decrease in placental permeability is undoubtedly due in considerable measure to the deposition of fibrinoid over the surface of the villi. All of these morphological changes provide an interpretation of the observed changes in transfer rate per unit weight placenta.

The placenta of man in Grosser's classification² belongs to the hemochorial group as do the placentas of rabbit, rat and guinea pig. According to the results of Mossman,⁹ the rabbit's placenta in the latter stages of pregnancy becomes

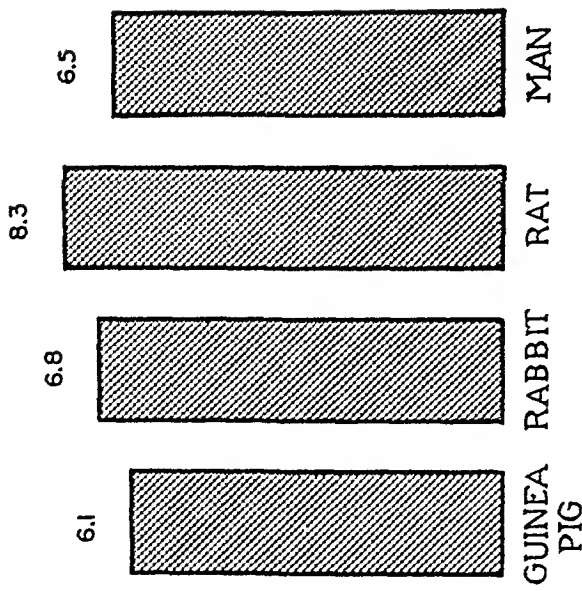


Fig. 3.—Variation of transfer rate of sodium per unit weight of placenta with the morphologic type of placenta. Values give the milligrams of sodium transferred across a gram of placenta per hour as observed in each instance at the middle of the ninth-tenth of pregnancy. The relative magnitudes of the transfer rates are indicated by the relative areas of the dotted rectangles. The diagrams indicate the number and kind of placental layers interposed between maternal and fetal circulation in each of Grosser's four groups.

EPITHELIO-CHORIAL

SYNDESMO-CHORIAL

ENDOTHELIO-CHORIAL

HEMO-CHORIAL

hemoendothelial and Mossman suggests that the same change may occur in the placentas of other rodents. Hard,¹⁰ however, has obtained evidence using the phosphatase reaction that the placenta of the guinea pig remains hemochorial throughout gestation. The results on transfer of sodium across the human placenta afford a functional test of its morphological similarity to other members of the hemochorial group. Fig. 3 presents schematically the tissue layers interposed between maternal and fetal circulations in Grosser's four groups. Above the diagrams of the placentas there is indicated graphically the amount of sodium transferred per Gm. placenta per hour at the middle of the ninth-tenth of gestation. It is evident that the four placental types can be readily distinguished from one another by the differences in their permeabilities. It is also evident that the permeability of the placenta of man to sodium agrees closely with other members of the hemochorial group. Once again in our studies on placental permeability, Grosser's classification has proved its extraordinary usefulness in the interpretation and integration of our results.

Our experience with the effect of disease, anesthesia and labor on the permeability to sodium is rather meager and suggests only tentative conclusions. The permeability of the placentas from five patients with hypertension and two with cardiac disease was found to be normal. The transfer rate was independent of the type of anesthesia. Two cases in which transfer rates were measured during labor, just prior to the time of delivery, showed normal rates indicating that placental function is not remarkably disturbed during this period. A reduction of transfer rate was noted in one of two cases of pre-eclampsia and the rate was low in the single case of twins which was studied. In our opinion, more experience with sodium and other tracer materials is needed in these several conditions before reliable conclusions about placental function can be drawn.

The use of tracer substances permits the study of that aspect of fetal nutrition which is concerned with the quality of substances supplied to the fetus as this is related to the growth requirements of the fetus. The lowest safety factor (ratio of the amount of a substance supplied to a unit weight of fetus to the amount of that substance retained by the unit weight of fetus in its growth) for sodium has been observed in the sow and has a value of 3.5.¹¹ The highest safety factor for sodium observed prior to the studies reported here is in the guinea pig and has an average value of 50.⁴ Man, in our experience, is unique in the extraordinarily high value of the safety factor which varies from 160 at twelve weeks to over 1100 at term; less than 0.1 per cent of the sodium which reaches the human fetus at term is retained, 99.9 per cent being returned to the maternal circulation. Man is unique also in that sodium is supplied at a constant rate, about 0.9 mg. per Gm. fetus per hour, from the twelfth week of pregnancy when the fetus is reproducing its weight at the rate of about 12 per cent per day to term when the daily per cent weight increase is only about 1 per cent. This is the single exception which has been found to the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus.⁹

Summary

1. Changes in rate of placental transfer per unit weight of placenta have been measured in normal pregnancies, using radioactive sodium, from the ninth week of gestation until term. The permeability of the placenta increases about 70 times during this period. The type of anesthesia was without effect on the rate which was also unaffected during labor immediately preceding birth. The permeability to sodium of the human placenta is like that of other members of the hemochorial group.

2. In a small series of cases, chronic hypertension and cardiac disease were without effect on the rate of transfer. One of two cases of pre-eclampsia showed a marked reduction of permeability.

3. The fetus receives across the placenta at the twelfth week of pregnancy 160 times, and at the fortieth week, 1100 times as much sodium as is incorporated in the growing tissues.

We are grateful to Dr. N. J. Eastman for his interest and generous cooperation.

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THE BABY AS A PROBLEM IN PREMATURE DELIVERY*

N. W. PHILPOTT, M.D., AND F. J. TWEEDIE, M.D., MONTREAL, QUE.

(From McGill University and Royal Victoria Hospital)

MUCH emphasis has been placed upon the importance of recognizing dystocia caused by malformation of the pelvic bones. This usually is referable to those cases near term who have a large-sized fetus and where there is a bony disproportion. But when we review figures of fetal deaths, we are impressed by the fact that a great proportion of these deaths occur in small babies where there is no bony disproportion. Soft tissue dystocia plays the important role.

Normal individuals possess a cervical canal which is the valve of the uterus. The cervical function in pregnancy is to hold the products of conception in their normal position. As maturity is approached the valve should release and allow the contents of the uterus to be expelled without causing undue obstruction. This is a gradual process which occurs in those weeks immediately preceding full term. Thinning of this lower uterine segment should normally be a non-painful procedure occurring before the onset of labor.

When labor occurs prematurely there is a great difference. The thick lower segment must be dilated by painful contractions. This is a tedious process and causes greater hazards to an immature fetus. Premature labor is frequently an accidental occurrence; it is unavoidable following some acute crisis or infection. These cases should be handled with extreme care.

The fetal mortality in vertex presentations where the baby is premature ranges far higher than those of mature infants. Complications are varied but the maximum danger occurs in the second stage of labor, relative to pressure of the soft malleable head against the resisting tissues of the pelvic floor. Mortality is still a great deal higher when the fetus presents as a breech, due to the fact that the diameters of the premature baby's hips or shoulders are less than those of the aftercoming head. Consequently, the head becomes compressed by a partially dilated cervix and by a lower tract which has not been adequately distended. A review of 500 breech cases in our Clinic showed interesting results.

Many obstetricians condemn bag induction. I agree that the indications are few. However, if labor occurs with the breech presenting, and the baby is premature of twenty-eight to thirty-four weeks' maturity, a bag induction should be considered as a proper dilator. In seven cases of this type, five live babies were obtained.

*Presented, by invitation, at a meeting of the Philadelphia Obstetrical Society, Feb. 6, 1947.

TABLE I. BREECH DELIVERY (500 CASES)

Total fetal mortality Cesarean or external version		13 per cent 26 cases	
	CASES	FETAL MORTALITY	
		NO.	PER CENT
Full term	403	31	7.6%
8 months	44	11	25%
7 months	27	22	81%

Certain conditions in the last trimester demand interruption of the pregnancy. Most obstetric techniques have been simplified during the last few years. But induction of labor has not been appreciably facilitated by improved methods. The obstetrician is frequently faced with the necessity of performing a premature delivery with no "near-perfect" method at his disposal.

TABLE II. INDUCTION OF LABOR BEFORE TERM IN ROYAL VICTORIA HOSPITAL

	1941-43 FETAL MORTALITY		1944-46 FETAL MORTALITY	
	NO.	PER CENT	NO.	PER CENT
Rupture of membranes	557	6.5%	528	6.2%
Medical	340	4.5%	374	4.7%
Medical & pituitrin	136	5.3%	116	7.0%
Bag induction	34	59.0%	19	57.0%

We are agreed that prophylaxis is the best form of treatment; possible prevention of those conditions which are prone to force induction should be further investigated. A nearer approach to maturity creates a better chance of survival unless some complicating factor outweighs this advantage.

Cesarean section is a quick and sure way of delivery. However, there are several pitfalls, especially in a French-Canadian environment. This operative procedure causes definite limitation to the size of the patient's family. But more important are the dangers of hemorrhage or sepsis which must always be considered. Sometimes this operation is the method of choice. It is the "trump card" only to be used at the proper time.

Delivery per vagina necessitates induction of labor. If the patient is approaching full term, most methods of induction are equally efficient. The difficulty encountered in the induction of labor is usually in direct proportion to the number of days the patient is lacking with reference to her appointed time of delivery. This is easily explained. Necessary stimulation to uterine contraction is lacking. In addition, the thinning of the lower uterine segment has not taken place. Induction of premature labor at any period in the last trimester should only be instigated on account of a definite medical indication. Too frequently labor is induced to please the patient, or even to accommodate the doctor who is in charge of the ease.

With reference to cephalopelvic disproportion cases, we do not induce labor unless the degree of disproportion is only moderate and the patient is near full term. Before induction, we make certain of the disproportion by vaginal examination; in addition we ascertain the condition of the cervix

and make certain that it will not offer too much obstruction. Simple rupture of the membranes is the method of choice except when there is marked disproportion and delivery by cesarean section is indicated.

Toxemia is fairly frequent in our hospital. Most of these cases are referred from outlying districts where they have had inadequate or no prenatal instruction. Prevention of the disease is the best approach when it is possible. Frequent antenatal visits and proper supervision are most essential. We heartily agree with Dr. Winslow Tompkins, in regard to high protein intake with reference to the prophylaxis and treatment of toxemia. Supportive treatment varies little from other clinics.

Induction of labor is carried out only when indicated. It is usually by simple rupture of the membranes. If the patient is severely toxic and she is not near term, we sometimes use the intraovular insertion of a small rubber bag of approximately 150 c.c. content. We fully realize that this type of delivery creates a possible 50 per cent fetal mortality. Cesarean section is occasionally performed for combined indications, and in the nephritic type of toxemia where future pregnancies do not promise any better fetal results.

Placenta previa and fetal mortality go hand in hand. Maternal hemorrhage causes fetal anoxia; there is the additional factor that prematurity also plays a role in producing a delicate baby. Even suspect cases are examined in the operating room. This is to prevent additional or needless loss of blood. The marginal type is most commonly treated by simple rupture of the membranes. More pronounced types of placenta previa are delivered by cesarean section. Anoxia in the baby is a frequent sequela of maternal blood loss. This is best treated by transfusing the mother with whole blood before operative procedures are instigated. This should be repeated as frequently as indicated. Administration of oxygen to the mother during operation is very beneficial.

Space does not permit discussion of Rh iso-immunization. Induction of labor or, sometimes, cesarean section before the baby becomes overwhelmed with antibodies is the wise procedure. Antibody studies can now give a fairly definite prognosis in most cases. A marked rise or variation in the agglutinating or blocking antibodies is indication for interruption of pregnancy any time after the baby is viable.

In June, 1946, Rivett reported successful results in hydramnios cases by means of repeated aspiration of fluid from the amniotic cavity. This is done through the abdominal wall with little risk. We have completed three cases since that time. One baby is normal, another had marked "clubfoot" and absence of several fingers and toes, while the third was a marked microcephalic with patent ventricular septum. This procedure is only indicated when the fetus is considered normal but small. If the development is not sufficient to assure viability, sometimes aspiration of excess fluid will enable the baby to reach the viable period.

Diabetes complicating pregnancy is a cause for worry. Fetal mortality is very high even in the controlled patient. Rabinowitch points out several important facts:—

1. Those patients only on diet control experienced as high a fetal mortality as the more severe types taking insulin.

2. The high incidence of diabetes plus toxemia due to marked increase in prolan found by White and Hunt could not be substantiated. Only 12 per cent of our cases showed evidence of toxemia.

3. Normal deliveries were usually postmature and were accompanied by the highest fetal mortality. Labor induced before term gave better results. The lowest mortality (8.3 per cent) was in the group where a cesarean was done before term.

TABLE III. DIABETES MELLITUS (RABINOWITCH)

Relationship Between Mode of Delivery and Fetal and Neonatal Mortality. (64 deliveries in Montreal)						
MODE OF DELIVERY	PRIMIPARAS			MULTIPARAS		
	NO.	DEATHS		NO.	DEATHS	
		NO.	PER CENT		NO.	PER CENT
Natural	3	2	66.6	13	4	30.7
Labor induced before term	11	2	18.1	4	1	25.0
Cesarean section	9	1	11.1	24	2	8.3
Total:	23	5	21.7	41	7	17.1

Many authors include syphilis as a common cause for prematurity. There have been 512 proved syphilitics in our obstetric service during the last thirteen years; this is an incidence of approximately 2 per cent. Practically every case has received adequate treatment during pregnancy. This is possibly why we do not see many premature babies due to syphilis. We had only three premature babies from syphilitic mothers in 1946. There were forty-one active syphilitics during the year. All cases had received antisyphilitic treatment.

The Baby

We have prepared certain charts which are self-explanatory. Table IV gives the general maternal and fetal mortality. During the six-year period from 1941 to 1946 there were 572 fetal deaths, and the clinical diagnosis is tabulated. Two hundred six of these deaths occurred in premature babies, an incidence of 36 per cent. The more accurate pathologic diagnosis is listed for 286 cases who had autopsy examinations. These excluded those cases where the infant was badly macerated and those where autopsy examination was refused by the parents. Of the 286 cases where autopsies were performed, 58 per cent occurred in premature babies:—

TABLE IV. 1941-1946

Total deliveries	15,691	
Maternal mortality	1941 to 1943	.17%
	1944 to 1946	.11%
Fetal mortality	1941 to 1943	3.7%
	1944 to 1946	3.5%

Clement Smith and others have shown that the premature baby differs greatly from the full-term infant. There is excessive accumulation of organic acids in the blood. Renal immaturity decreases kidney function, and there is a limitation of water available for urinary secretion. Hepatic immaturity

causes decreased liver function. Blood studies show a comparative anemia with a predisposition to developing anoxia and hemorrhage in the brain and liver. The immature lung is frequently associated with patchy atelectasis which predisposes to subsequent respiratory infection. Altogether the premature baby is a liability.

Antenatal pediatrics is a new term, but the significance is old. We are all agreed that the general physical condition of the pregnant woman is often reflected in the condition of the offspring. This is especially true relative to the premature baby. Prophylaxis of preventable conditions frequently is assured by means of adequate antenatal care. Nutrition is important in all cases. Abnormal findings should be heeded and the complication should be promptly treated. Judicious use of sedatives during labor, type of delivery and well-chosen anesthetic all play an important role in the result obtained.

It has been shown that the incidence of premature infant mortality varies inversely to the size of the babies. We also emphasize the fact that deaths in premature infants become progressively less frequent with each hour of life. Over 50 per cent of all neonatal deaths in premature babies occur during that first twenty-four hours following delivery. Some of these deaths are preventable. This is relative to: conditions caused by anoxia, aspiration of mucus or other fluids, insufficient incubation, and too many contacts.

The obstetrician and pediatrician should work in harmony. Their combined invaluable experience is most essential to obtain good results. This necessitates more than an average knowledge relative to the care of the newborn baby; both obstetric and pediatric interns should receive adequate instruction in the care of the newborn baby. Beck has pointed out the advantages of a definite system. It has also been emphasized in the report of the Illinois State Plan where excellent results were obtained by developing an organization which is supervised jointly by the obstetrician and the pediatrician.

It should be emphasized, however, that the authority and interest of the obstetrician must be maintained in the care of the newborn infant. This is essential due to the fact that effects of pregnancy, labor, and delivery play the major role in the eventual outcome of the offspring. Most fetal deaths occur during that period when the obstetrician is in complete charge, regardless of what system is followed during the neonatal period.

Our hospital has a staff pediatrician who supervises the routine in all nurseries. A resident who is trained in the care of the newborn is in charge of all babies. He reports to the staff pediatrician as well as to the obstetrician who is in charge of the individual case. This resident is present at all difficult deliveries such as cesarean births, difficult forceps cases, and those complicated by placenta previa or toxemia. He supervises and treats all babies from birth until the time of discharge.

Treatment of the premature baby is most important. There are two phases: (1) First hour of life, and (2) Neonatal period in the nursery.

Very small babies are fed every two hours. Poor feeders have a three-hour schedule, and good feeders receive feedings every four hours.

Clysis of plasma or glucose and saline is given for dehydration or to stimulate weight gain. The hemoglobin is estimated at least every seven days. Iron therapy is given when indicated. Whole blood transfusions are used when conditions warrant; this is a fairly common procedure in the premature nursery, and the indications have become more numerous.

Our premature nursery has completed three years in operation. For this reason I have taken two three-year periods for comparison. These periods are 1941 to 1943 and 1944 to 1946, inclusive.

The most significant improvement is in the fewer number of deadborn infants in the period from 1944 to 1946. General fetal mortality as well as premature deaths have decreased slightly. It should be emphasized, however, that the incidence of complicated cases has increased considerably in the last three years in our clinic. This is due to the fact that outside doctors would rather not handle this type of case and they are referred to our hospital. For example our admissions of hemolytic disease of the newborn have increased over 200 per cent.

Many of the deaths could not be prevented, but a great number are included which should be considered as preventable. It is interesting to note that only three babies died from effects of syphilis. There were 206 active syphilitics delivered in this series. Only six did not receive antisyphilitic treatment.

TABLE V. PREMATURE BABIES WEIGHING 1,000 TO 2,500 GM.

Total number		912
Incidence.		5.7%
Mortality	1941 to 1943	24.3%
	1944 to 1946	21.0%
Five (5) babies under 1,000 gm. survived.		

TABLE VI. SUMMARY OF INFANTS UNDER 1,000 GM. AT BIRTH

CASES	BIRTH DATE:	BIRTH WEIGHT (GRAMS)	DISCHARGE DATE:	DISCHARGE WEIGHT: (GRAMS)
1. Baby S.	Oct. 6/44	660	Feb. 13/45	2340
2. Baby Bl.	Dec. 10/44	940	Mar. 1/45	2400
3. Baby Bll.	Dec. 10/44	900	Mar. 1/45	2340
4. Baby D.	Aug. 2/45	930	Nov. 29/45	2340
5. Baby P.	Sept. 15/46	990	Dec. 21/46	2660

The premature babies were classified only as those between 1,000 to 2,500 Gm. This coincided very well with estimation from the twenty-eighth to the thirty-sixth week of pregnancy. However, there were seventeen babies admitted to the premature nursery, and they all weighed less than 1,000 Gm. Five of these infants are still alive; the smallest weighed 660 Gm. at birth and it is now over two years of age. This is particularly significant in view of the fact that Haas reports only fifty-seven cases in the literature which survived and also weighed less than 1,000 Gm. at birth.

Our premature mortality rate is slightly higher than figures given by the Long Island College Hospital and the Hahnemann Hospital of Philadelphia. But we have had better success with the very small babies. We cannot boast of a great reduction in mortality during the last three-year period seeing that it dropped only 3 per cent. However, the reduction is important due to the fact that incidence of complicated cases in our clinic has increased considerably during this three-year period. In addition, it should be mentioned that several babies were considered as nonviable in the 1941-43 period. There were 20 babies which were approximately 1,000 grams but they were not weighed. These died shortly after birth, and several of them were indexed as nonviable. In the period from 1944-46 all babies were weighed and the uncorrected mortality includes every baby weighing between 1,000 and 2,500 grams.

Summary

1. Induction of premature delivery should be carried out only on account of a definite indication.
2. Adequate equipment and trained personnel are essential for a premature nursery.
3. Breast milk bank and blood bank facilities are useful adjuncts.
4. Fetal mortality can best be improved by the combined efforts of the obstetrician and pediatrician.

We are grateful for the cooperation and suggestions of Dr. Graham Ross, Pediatrician-in-charge.

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Discussion

DR. CARL BACHMAN.—I wish to emphasize the notion that the premature infant is handicapped not only by its prematurity, but also by the fact that, in the great majority of instances, it is also an ill or damaged infant. Of the factors which militate against its survival, its prematurity per se is perhaps the least important.

The pathologic factors are twofold. The first is the disease or abnormality of the mother, or of the ovum itself, which is responsible for interrupting the infant's intrauterine development prematurely. Who can say that the fetus of a toxic mother, or of one who suffers an antepartum placental hemorrhage, is not likely to be handicapped by these factors? Yet if one reviews one's experience with premature delivery, one must be struck by the fact that the overwhelming majority of them occur, whether spontaneously or by design, because of abnormalities of this character accompanying the gestation.

The second factor is the frequently tedious, and therefore often traumatic character of premature labor and delivery. Some of the factors which make it so have been mentioned by Dr. Philpott. Because of them, our Staff at the University of Pennsylvania have become increasingly loath to resort to induction of premature labor when there is a legitimate in-

dication for interrupting pregnancy, but prefer to do an abdominal delivery. We prefer it because we have found that more infants survive such a method of delivery, yet the maternal risk has not been increased. We shall continue to do this, under these circumstances, until and unless methods can be developed for inducing and obtaining premature labors that are superior to current ones.

DR. PHILPOTT (closing).—I think Dr. Baehman and I are in agreement with regard to induction of labor and the results thereof. I would only like to define our attitude in Montreal regarding inducing labor. We are in a predominantly French Canadian community and that must be borne in mind. My reaction to cesarean section is that a good many can do one or two cesareans, but not eight or nine in the same patient. Our community is very orthodox in religion. They do not believe in ligation of the tubes and we do not do more cesareans on that account. One or two cesareans can be done safely, but beyond that it is dangerous. Over 50 per cent in the community are Roman Catholics. Most will not consent to ligation of the tubes, and it is necessary to follow the course I have presented, and we have resorted to that. The fewer labors we induce the better results we will get. The premature baby is another problem. It is often a sick baby, it has gone through a tedious labor, and as a result of premature delivery is not fully developed, the renal system and the various other systems are immature, and all in all it is an entirely different problem from the full-term baby. With reference to Dr. Montgomery's question, we have been very pains taking and definite about prematurity.

THE FATE OF THE LIVING VIABLE BABIES IN EXTRAUTERINE PREGNANCIES

MAX SUTER, M.D., JACKSONVILLE, FLA., AND CELESTE WICHSEK, M.D.,
NEW ORLEANS, LA.

(From the Departments of Obstetrics and Gynecology, Louisiana State University School of Medicine and Charity Hospital of Louisiana)

THIS paper was written with the idea of determining, as nearly as possible, from the limited clinical material available at Charity Hospital of Louisiana, at New Orleans, and from a survey of the literature the fate of the viable babies delivered from extrauterine pregnancies. Only cases of twenty-eight or more weeks' gestation with babies born living were selected. Forty-one additional cases of living, viable babies in abdominal pregnancies are presented graphically from the literature to supplement those recorded by Sittner,⁶ Hellman and Simon,² and Mitra.⁴ Four new cases are presented from Charity Hospital, at New Orleans, in addition to those recently reported by Beacham and Beacham.¹

Winckel⁷ in discussing the deformities of extrauterine pregnancies stated that 75 per cent of all the deformed children included deformities of the head, half of them deformities of the lower extremity, and 40 per cent deformities of the upper extremity. The more sheltered thorax, abdomen, and genitourinary system were deformed in only 3 or 4 per cent of the babies. Of 316 living, viable babies reviewed by Hellman and Simon² in 1935 from the world literature, including those previously reported by Sittner, a specific statement as to the development of the babies was made in only sixty-four cases. Of these, thirty, or 46.6 per cent, were found to be deformed. One hundred fifty, or 44.3 per cent, of the babies survived for eight days or more, and of these a specific statement as to the development was made in forty-one babies; fifteen, or 36.6 per cent, were found to be deformed. Stabler,⁵ in 1938, reviewed 266 cases from the world literature. Of 266 living, viable babies delivered from abdominal pregnancies, 152, or 57.1 per cent, lived for eight days or more. The fate of only one was undetermined. Twenty-eight, or 10.5 per cent, of these babies were recorded as being deformed. Lelling,³ in reviewing 106 cases in 1938, found that development was mentioned in only 82 of the 106 babies. Of these, thirty-two, or 39 per cent, were recorded as deformed. Mitra,⁴ in reviewing the world literature on advanced extrauterine pregnancies in 1942, found that of 179 extra-uterine pregnancies of more than five months' gestation only 23.5 per cent delivered living, viable babies. Of these, a specific statement as to the development was made in thirteen, ten of which were recorded as being deformed. Beacham and Beacham,¹ in a report of twenty abdominal pregnancies from Charity Hospital, at New Orleans, found that only three, or 15 per cent, delivered living, viable babies.

In our review of forty-one additional cases in the literature we found that a specific statement as to the development was made in thirty-one babies. Twelve, or 38.7 per cent, of these babies were found to be deformed. Ten, or 24.3 per cent, of the babies died before the eighth day.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital.

Case Reports

CASE 1.—E. P. The patient, a Negro female, gravida i, para 0, whose last menstrual period was Nov. 23, 1944, was admitted to Charity Hospital on July 25, 1945, with the chief complaint of pain in the lower abdomen, and vomiting. When she was three to four months pregnant, the patient had an attack of severe lower abdominal pain associated with fainting from which she recovered spontaneously.

The patient's blood pressure was 135/100. Her abdomen was the size of an eight months' pregnancy, and fetal parts were quite superficial. The abdomen was markedly tender. Fetal heart tones were 140 in the left lower quadrant. Sterile vaginal examination was done. The cervix was pushed forward, soft, long, and patulous. Membranes or fetal parts were not felt through the cervical os. A shoulder was felt posterior to the cervix. Urinalysis was negative. Hemoglobin was 10 grams. X-ray revealed cephalic presentation with back to right. No uterine shadow was seen.

Preoperative diagnosis: abdominal pregnancy.

Laparotomy was performed on July 25, 1945. Uterus was found to be the size of a ten weeks' pregnancy, with a 5 cm. fibroid extending to the left. A male infant was free in the abdominal cavity without a sac. A small amount of fluid was found in the abdominal cavity. Male baby weighed $4\frac{3}{4}$ pounds, and had a deformed head and clubfeet. He was in poor condition after birth and died the same day. The cord was tied off close to the placenta and the abdomen was closed without drainage, leaving the placenta in situ.

Postoperative course was afebrile after the first day, and the patient was discharged on the seventeenth day, at which time the placental mass had not regressed in size.

Patient was readmitted on Feb. 7, 1946, with the chief complaint of pain in the abdomen. She was afebrile during the stay in the hospital and was operated on Feb. 19, 1946, for removal of retained placenta. The placenta was found to be attached to the cul-de-sac, posterior surface of the right broad ligament, lateral wall of the pelvis, posterior pelvic wall, rectosigmoid, and mesoappendix. In order to remove the placenta it was necessary to do a subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy. The patient was discharged on Feb. 28, 1946, in good condition.

CASE 2.—V. R. The patient, a 28-year-old Negro female, whose last menstrual period was April 1, 1946, was admitted to Charity Hospital on Jan. 8, 1947, with a history of recurrent abdominal pains every two to three minutes, nausea, and vomiting. On September 17 the patient had an episode of bleeding. Since September, 1946, she had been having periodic attacks of pain in the lower abdomen more severe on the right side, which were relieved by vomiting and aggravated by any activity. The patient said that she felt the baby move only on the right side.

Blood pressure was 110/80. Heart and lungs were negative. Abdomen was enlarged to the size of a term pregnancy, vertex presentation, head floating. Fetal heart tones were best heard in the right lower quadrant, and their rate was 152. The patient was recorded as having hard pains every three minutes. Urinalysis was essentially negative. Hemoglobin was 9.5 grams.

Diagnosis of breech presentation was made which was confirmed by x-ray. X-ray also showed a peculiar shaped occiput in left flank.

On Jan. 9, 1947, the cervix was found to be soft, long, and would barely admit one finger. Exploration of uterine cavity revealed no membranes nor fetal parts. It was found to be about 10 cm. long.

Patient had a laparotomy on Jan. 9, 1947, with preoperative diagnosis of abdominal pregnancy. When the abdomen was opened, the fetal sac was found in the abdominal cavity. This was opened and a living, male infant weighing 6 pounds was delivered by breech extraction. The baby had a plastic deformity of the head and a right clubfoot, and contraction deformities of both arms. The placenta was attached to the bowel, the omentum, and the left cornual portion of the uterus. The placenta was removed with minimum amount of bleeding. The abdomen was closed without drainage.

Postoperative course was essentially afebrile. Five-month check-up revealed that both mother and baby were getting along well.

CASE 3.—E. McC. The patient, a 23-year-old Negro female, gravida i, para 0, whose last menstrual period was June 7, 1946, was admitted to Charity Hospital on March 23, 1947, with the chief complaint of pain in the abdomen for the past two days.

The heart and the lungs were negative. The abdomen was that of a breech at term. Fetal heart tones were 140 and best heard in left upper quadrant. There was marked costovertebral tenderness. During her stay in the hospital, the patient developed enlargement of the abdomen with marked dyspnea.

Vaginal examination disclosed the cervix undilated and uneffaced. No membranes nor fetal parts were felt through the pelvis.

Temperature was 101° F., pulse 130; blood pressure 130/72. Urine was essentially negative. Hemoglobin was 11.8 grams. X-ray revealed one fetus outside of pelvis, breech presentation. No uterine wall could be made out.

Preoperative diagnosis: Abdominal pregnancy at term.

Patient had a laparotomy performed on March 25, 1947, at which time the placenta was found attached to the left cornual portion of the uterus. Some uterine muscle fibers extended up alongside of the fetal sac, but did not entirely cover it. When the sac was opened, it was found to be made up of three definite layers; the outside one was rather fibrous in character. The sac was opened and an 8 pound 15 ounce apparently normal living male child was delivered, who died in a few minutes. In order to remove the placenta, a left salpingo-oophorectomy and supracervical hysterectomy were necessary. The mother was discharged in good condition on the tenth postoperative day.

CASE 4.—D. T. The patient, a 29-year-old Negro female, gravida v, para iii, had not menstruated since her last pregnancy in 1946. She was admitted to Charity Hospital on May 9, 1947, with a history of having had convulsions that morning and having had some sedation given her by her private physician. On admission she was semistuporous and complained of pain in the lower abdomen. She had a productive cough and expectorated blood-tinged sputum. She had been dyspneic for some time.

Temperature was 99.4° F.; pulse 160; blood pressure 164/128. There was marked edema of legs and moderate edema of anterior abdominal wall. The lungs had a few râles at both bases. The heart was enlarged 3 cm. to the left midclavicular line. The abdomen was the size and contour of a term pregnancy. No definite fetal heart tones were heard.

At vaginal examination the cervix could not be felt because it was high and anterior. There was a firm mass about 10 cm. in diameter filling the cul-de-sac.

The urine showed three plus albumin; hemoglobin 11.5 Gm.; venous pressure 115 millimeters of water. X-ray revealed a fetus lying between transverse and in a breech. An electrocardiogram was strongly suggestive of myocardial disease. Kline test was positive.

TABLE I. SUMMARY OF CASES SINCE 1930

DATE OF OPERATION	OPERATOR	PLACE OF OPERATION	RESULT TO MOTHER	STATUS OF FETUS	SPECIAL NOTES; BIBLIOGRAPHY
Feb. 2, 1930	Reeb	Strassburg, Germany	Recovered	32 weeks; lived; normal	Kries, J. Reb.: <i>Frang. de Gynec. et Obst.</i> 32: 89, 1937.
Dec. 29, 1930	Lafloque	Richmond, Va.	Recovered	40 weeks; lived; normal	Ware, H. H.: <i>New York State J. Med.</i> 36: 1943, 1936.
Mar. 1, 1931	Gushue and Taylor	Tailhook, Formosa	Died (from ileus and shock)	44 weeks; female, well formed, normal, 7 lbs.	Gushue-Taylor: <i>Brit. M. J.</i> 1: 640, 1942.
Apr. 16, 1932	McNeile	Los Angeles, Calif.	Recovered	28 weeks; living; no deformities	McNeile, L. G.: <i>West. J. Surg.</i> 45: 119, 1937.
Dec. 11, 1932	Beal and Cassell	Gemdar, South India	Recovered	40 weeks; gasped and died; deformity of left foot; 7 lbs.	Beal, A. M., and Cassell, N. S.: <i>J. Iowa M. Soc.</i> 30: 445, 1940.
Sept. 6, 1933	Ziegler	Pittsburgh, Pa.	Recovered	40 weeks; living male, normal, 7 lbs. 2 oz.	Eiseman, J. R., and Ziegler, C. E.: <i>J. A. M. A.</i> 104: 2175, 1935.
July 20, 1934	Eula and Eno	Shanghai	Died	40 weeks; asymmetry of head; deformity of right knee; female, 7 lbs. 6½ oz.	Eno, E., and Towers, A. E.: <i>Chinese M. J.</i> 51: 33, 1937.
Jan. 9, 1935	Woods	Augusta, Ga.	Died (14 hr.)	38 weeks; living; normal, 5 lbs. 2 oz.	Woods, E. B.: <i>AM. J. OBST. & GYNEC.</i> 32: 155, 1936. (Autopsy done.)
Feb., 1935	Bondurant	Cairo, Ill.	Recovered	40 weeks; living, normal, 4¾ lbs.	Bondurant, F.: <i>Illinois M. J.</i> 71: 480, 1937. (Combined full term; extra and intrauterine gestation. Intrauterine child had congenital syphilis; weight 3½ lbs.; lived 5 days.)
April 15, 1935	McNeile	Los Angeles, Calif.	Recovered	24 weeks; lived 24 hours; normal	McNeile, L. G.: <i>West J. Surg.</i> 45: 119, 1937.
June 11, 1935	Wilson	Dubau, India	Recovered	32 weeks; lived; normal, 5¼ lbs.	Wilson, A. S.: <i>Proc. Roy. Soc. Med.</i> 29: 1651, 1936.
Sept. 11, 1935	Anderson	Lacknow, India	Recovered	4 weeks; lived 15 min.; 6 lbs.	Anderson, M.: <i>Brit. M. J.</i> 2: 589, 1936.
Sept. 11, 1935	Colistro	Pasteur Hospital Uruguay	Died	40 weeks; baby alive at operation	Colistro: <i>Arch. Urug. de Med. Cir y Especialid</i> 14: 141, 1939. (Did not say if baby continued to live.)
Dec. 3, 1935	MacGregor	Brooklyn, N. Y.	Recovered	38 weeks; living; not normal, 2,660 Gm.	MacGregor, A. S.: <i>AM. J. OBST. & GYNEC.</i> 34: 1030, 1937.

Feb. 1, 1936	Lailey	Toronto, Canada	Recovered	44 weeks; lived; had one club-foot; no other deformity; 11 lbs. 1 oz.	Lailey, W. W.: Canad. M. A. J. 36: 67, 1937.
Mar. 12, 1936	Lelling and Leudemann	Barbarakrankenhaus, Germany	Died	7 mo.; not resuscitated; club-foot	Lelling, E.: Zentralbl. f. Gynäk. 62: 2209, 1938.
Mar. 23, 1936	Shen Shi Yung	Shanghai	Recovered	48 weeks; died in 6 hr.; head asymmetrical; cleft palate	Eno, F., and Towers, A. E.: Chinese M. J. 51: 33, 1937.
June 7, 1936	Hoffman	Charleston, West Va.	Recovered	40 weeks; lived $\frac{1}{2}$ hr.; baby cyanotic; 4 lbs. 10 $\frac{3}{4}$ oz.	Hoffman, W. E.: West Virginia M. J. 33: 496, 1937. (Child has a marked distortion of head; nose is flattened against face, and right nares is closed; flexion deformity of right elbow; right foot is everted.)
June 25, 1936	Salamanca	Mexico City	Recovered	39 weeks; lived 17 hr.; 6 lbs. 2 oz.	Salamanca, A. G.: J. Internat. Coll. Surgeons 3: 271, 1940.
May 1, 1937	Brack	Grainberg	Recovered	Living; normal; 3,300 Gm.	Stavenhagen, Med. Klin. 33: 1609, 1937.
June 10, 1938	Harkness	Mevanza, Tanganyika Territory	Died	40 weeks; not resuscitated; normal, 7 $\frac{1}{2}$ lbs.	Harkness, J., and Fairfax, B.: Brit. M. J. 2: 1044, 1938. (There was question if baby was living. Mother died at surgery. Head slumped into vagina.)
Aug. 27, 1938	Hamblen	Spokane, Wash.	Recovered	40 weeks; lived 3 hr.; normal, 5 lbs. 2 oz.	Hamblen, R. N.: West. J. Surg. 48: 310, 1940.
Sept. 12, 1938	Hains	Bundaberg, Queensland	Recovered	Right hip was turned in; 3,200 Gm.	Hains, I. C.: M. J. Australia 1: 268, 1939.
March, 1939	Cunningham	Ireland	Recovered	36 weeks; lived; 4 lbs. 4 oz.	Cunningham, J. F.: Irish J. M. Soc., 846, 1939.
Mar. 18, 1939	White and Clark	Asheville, N. C.	Recovered	40 weeks; lived; normal	White, R. A.: North Carolina M. J. 2: 87, 1941.
Mar. 28, 1939	Nicodemus	Danville, Pa.	Recovered	38 weeks; viable; lived; female 4 lbs. 9 oz.	Nicodemus, R. E., and Carrigg, L. G.: Am. J. Obst. & Gynec. 39: 153, 1940.
July 18, 1939	Mayer and Marino	New Orleans, La.	Recovered	42 weeks; lived; normal, 7 lbs. 13 oz.	Beacham, W. D., and Beacham, D. W., Obst. & Gynec. Survey 1: 777, 1946.
Aug. 4, 1939	Sprague and Chappel	Athens, Ohio	Recovered	36 weeks; lived 48 hr.; female, 7 lbs. 2 oz.	Sprague, J. R., and Chappel, M. R.: Ohio State M. J. 36: 520, 1940. (Child had asymmetrical head and equinus varus.)
Nov. 16, 1939	Renner	Goodland, Kan.	Recovered	40 weeks; normal, 6 lbs. $\frac{3}{4}$ oz.	Renner, M. J.: J. Kansas M. Soc. 42: 245, 1941.

TABLE I—CONT'D

DATE OF OPERATION	OPERATOR	PLACE OF OPERATION	RESULT TO MOTHER	STATUS OF FETUS	SPECIAL NOTES; BIBLIOGRAPHY
Oct. 4, 1939	Nicholls	Norfolk, Va.	Recovered	-40 weeks; male, normal, 10 lbs. 3 oz.	Nicholls, R. B.: AM. J. OBST. & GYNEC. 42: 341, 1941.
Feb. 25, 1941	Lin	Foochow, Fukien	Recovered	-40 weeks; lived 2 hr.; asymmetrical face, right elbow; knee could not be straightened	Lin, A. Y.: Chinese M. J. 62: 383, 1945.
July 26, 1941	Slatover	Manchester, England	Recovered	-40 weeks; lived; normal female, 8 lbs. 10 oz.	Slatover, M. L.: Brit. M. J. 1: 669, 1942.
Sept. 30, 1941	Guerriero and Hughes	New Orleans, La.	Recovered	-32 weeks; living	Beacham, W. D., and Beacham, D. W.: Obst. & Gynec. Survey 1: 777, 1946. (L-41-42400, Case XII.)
Oct. 1, 1941	Strumpf	Jacksonville, Fla.	Recovered	-29 weeks; living; full term?	Strumpf, I. J.: AM. J. OBST. & GYNEC. 45: 350, 1943.
Dec. 31, 1941	Lucas	Walsall, England	Recovered	-34 weeks; lived; normal male, 5 lbs. 10 oz.	Lucas, C. F.: Brit. M. J. 1: 722, 1942.
Mar. 6, 1943	Rabago	General Hospital, Mexico City	Recovered	-28 weeks; twins, one in uterus; one in cul-de-sac; female in cul-de-sac lived	Rabago: Cir. y. Cirujanos 12: 27, 1944.
Dec. 18, 1943	Rose	Miami, Fla.	Recovered	-34 weeks; lived; normal; 5 lbs. 2½ oz.	Rose, M. J.: J. Florida M. A. 31: 475, 1945.
Mar. 7, 1944	Greene	Memphis, Tenn.	Recovered	-40 weeks; lived only short period	Greene, G. G.: South. M. J. 38: 747, 1945. (Case No. 3.)
Feb. 19, 1945	Morgan and Keevil	Newport, Montreal	Recovered	-36 weeks; lived 1 hr.; male	Morgan, R. G., and Keevil, N. L.: Brit. M. J. 2: 649, 1945.
June 7, 1945	Goodin	Port William Ontario	Recovered	-40 weeks; male, 7 lbs.; lived 21 hr.; died of atelectasis	Goodin, P.: Canad. M. A. J. 54: 483, 1946. (Baby was a livid-grey color and could not be made to cry.)
July 8, ?	Novey	Baltimore, Maryland	Died	-40 weeks; living; marked bilateral deformities of feet; weight 5 lbs. 8 oz.	Novey, M. A.: Surg., Gynec. & Obst. 66: 671, 1938. (Case 4, A. B., Negro, aged 31 years.)

A laparotomy was performed on May 13, 1947, with preoperative diagnosis of abdominal pregnancy versus uterine fibromyomas with intrauterine pregnancy. The fetal membranes were found free in the abdominal cavity. The membranes were opened and a grossly deformed living baby was found which died in thirty minutes. The placenta was attached to the uterus posteriorly between the broad ligaments, to the right iliac fossa, posterior abdominal structures, and small bowel. The cord was cut short. The placenta was left intact and the abdomen was closed without drainage.

On her sixteenth postoperative day the patient is in good condition but is still febrile.

Conclusions

Only about one-fourth of all the extrauterine pregnancies diagnosed after the fifth month of gestation will result in viable, living babies. About one-third of all these living, viable babies delivered from extrauterine pregnancies will have major or minor deformities including those which were incompatible with life. Approximately half of all the viable, living babies delivered from extrauterine pregnancies will survive eight days or more.

Summary

All the available literature on extrauterine pregnancies resulting in viable, living babies is reviewed to determine their ultimate fate.

Forty-one cases are tabulated from the literature to supplement those previously summarized.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital of Louisiana, at New Orleans.

The authors wish to acknowledge their appreciation to Drs. Adolph Jacobs, D. W. Goldman, and E. L. King for use of cases on their services.

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ANTEPARTUM HEMORRHAGE*

ROBERT A. KIMBROUGH, M.D., PHILADELPHIA, PA., AND BROCK D. JONES, M.D.,
NORFOLK, VA.

(From the Division of Obstetrics and Gynecology, Pennsylvania Hospital)

THE first section of this presentation is based upon a survey of the cases of premature separation of the normally implanted placenta occurring in the Philadelphia Lying-in Hospital during the twelve-year period from 1934 to 1945. Cases presenting this complication prior to the twenty-eighth week of pregnancy have been excluded from the study.

TABLE I. INCIDENCE OF PREMATURE SEPARATION OF THE PLACENTA
Philadelphia Lying-in 1934-1945 (inclusive)

Total number of deliveries	28,288
Number of cases of abruptio	113
Incidence of abruptio	1 in 250

The wide variation in the recorded incidence of abruption of the placenta can be accounted for by the strictness of the criteria which one establishes for the inclusion of cases. For the purpose of this study we have excluded all cases in which there was no clinical evidence of separation. An almost equal number was eliminated in which the condition was recognized only after delivery of the placenta by the discovery of small retroplacental clots, or minute organized areas of separated placental tissue. The group of 113 cases is composed, therefore, only of those presenting one or more of the following typical clinical manifestations of placental separation: continuous uterine pain, tenderness and tenderness of the uterus, evidence of intrauterine hemorrhage, or frank external bleeding.

TABLE II. ETIOLOGICAL FACTORS IN PREMATURE SEPARATION

	NUMBER	PER CENT
Toxemia of late pregnancy	54	48
Unknown	59	52
Total	113	100

Hypertension and/or albuminuria were found in almost one-half of the entire group, and in many of those in which the etiology is recorded as unknown, rather typical symptoms such as abnormal gain in weight and edema, strongly suggested the presence of toxemia. A pre-existing hypertension in many others may have been masked by a fall in blood pressure incident to hemorrhage. A definite history of trauma was elicited in only one instance; in this patient the co-existence of toxemia was a more likely cause of the separation.

*Read by invitation before the South Atlantic Association of Obstetricians and Gynecologists February 8, 1947, at Savannah, Georgia.

TABLE III. TIME OF OCCURRENCE OF ABRUPTIO

	CASES	PER CENT
Before labor	63	56
During labor	50	44
Total	113	100

TABLE IV. SEVERITY OF CASES OF ABRUPTIO

Mild	35
Moderate	39
Severe	39
Total	113

The mild cases were those occurring, almost without exception, during labor, manifested by somewhat more than usual bleeding, some increase in uterine tension, and, occasionally, evidences of slight or moderate fetal distress. In this group there were no maternal deaths. The severe cases were those in which there was evidence of a large concealed or external hemorrhage.

TABLE V. METHOD OF DELIVERY IN ABRUPTIO; 1934-1945

		CASES	PER CENT
Vaginal Delivery		47	42
Forceps	23		
Spontaneous	19		
Podalic version	1		
Breech extraction	4		
Abdominal Delivery		66	58
Cesarean section	62		
Porro cesarean	4		
Total number of cases		113	100

The choice of treatment in cases of abruptio is dependent upon several factors, chief among which are the severity of the symptoms, the general condition of the patient, whether or not the patient is in labor, and, most important, the degree of cervical dilatation. In dealing with the milder degrees of separation occurring in the course of labor, in which neither the mother nor the baby present evidence of distress, it is rarely necessary to interfere with the normal course of labor. This is evidenced by the fact that of the forty-seven patients with mild or moderate degrees of separation who were delivered by forceps, breech extraction, or spontaneously, only one patient died; in this case acute hepatitis was primarily responsible for death. As seen in the following table, three-fourths of the patients whose abruptio occurred during labor were delivered vaginally.

TABLE VI. METHOD OF DELIVERY ACCORDING TO ONSET OF LABOR

	CASES	PER CENT
Abruptio during labor	50	
Cesarean section	12	24
Vaginal delivery	38	76
Abruptio before labor	63	
Cesarean section	54	86
Vaginal delivery	9	14

On the other hand, the more urgent cases, because of extreme loss of blood and shock require that the uterus be emptied by the quickest method compatible with safety to the mother. Not until the uterus is empty can firm contraction

of the uterus close the bleeding sinuses of the placental site. If, therefore, the separation is of major degree and if the patient cannot be immediately and safely delivered by simple measures from below, we feel that cesarean section is the treatment of choice. In the more severe cases cesarean section is done in the interest of the mother, even though the child is known to be dead. Before instituting any procedure for delivery, it is imperative that the patient be treated for shock and that lost blood be adequately replaced by transfusion. A fine point of judgment is required in determining how long to postpone operative measures while awaiting reaction from shock. No arbitrary rules can be enunciated, as every case must be individually considered.

TABLE VII. MATERNAL MORTALITY FROM ABRUPTIO; 1934-1945

	NUMBER	PER CENT
Number of cases of abruptio	113	
Number of maternal deaths from abruptio	2	1.8

TABLE VIII. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY; 1934-1945

Vaginal delivery	1 death in 47 cases	2.1%
(Patient died of acute hepatitis)		
Cesarean section	1 death in 66 cases	1.5%
Total maternal mortality	2 deaths in 113 cases	1.8%

Removal of the uterus was deemed advisable in but four of the 66 patients who were treated by cesarean section. We do not remove the uterus simply because of its darkened appearance from extravasation of blood, but only if it fails to contract following its evacuation. There was no fatality incident to this procedure.

Following delivery, attention must be given to the likelihood of postpartum hemorrhage. Many of these uteri fail to remain firmly contracted, and a relatively small amount of bleeding will be poorly tolerated by the patient who has already suffered a considerable loss of blood. Firm packing of the uterus and vagina is urgently indicated, on the least provocation, as is also the intravenous administration of oxytocics.

TABLE IX. GROSS FETAL MORTALITY FROM ABRUPTIO; 1934-1945

Total number of cases of abruptio	113	
Total number of fetal deaths	39	35%
Stillborn	19	
Neonatal deaths	20	
(19 of the 39 dead babies weighed less than 4 pounds)		
Corrected fetal mortality		21%

Since fully one-fourth of the babies were dead in utero at the time of admission to the hospital, and since nineteen of the babies weighed less than four pounds, the total uncorrected mortality rate of 35 per cent is better than had been anticipated. There is no doubt, however, that this could be substantially reduced by more prompt recognition of the significance of the symptoms on the part of both patient and physician.

The following are brief summaries of the two fatal cases of abruptio placentae.

CASE 1.—A toxic patient had profuse bleeding and signs of abruptio at the eighth month, about four hours after the onset of labor. She was delivered of a six-pound stillborn child by forceps. Free postpartum bleeding continued

despite packing of the uterus and vagina. A total of 2,250 c.c. of whole blood and infusions of glucose were given. The patient died six days after delivery, of acute hepatitis as proved at necropsy. This death was considered in staff conference as nonpreventable.

CASE 2.—An 18-year-old Negro patient, whose early prenatal course was eventful, was admitted in mild pre-eclampsia at full term. The fetal heart sounds could not be heard. Her cervix was not dilated and her pains were irregular until one hour after admission. At that time her membranes ruptured spontaneously; she had a moderate amount of external bleeding. One hour later she had definite evidence of concealed hemorrhage and cesarean section was elected. In the hour and a half elapsing before operation, her blood pressure fell from 140/90 to 80/50. Because of this, an infusion of plasma was started simultaneously with the operation. A stillborn child and the completely separated placenta, along with 2,000 c.c. of blood were evacuated from the uterus. The uterus was packed and routine closure was performed. A transfusion of 500 c.c. of whole blood was given, but the patient failed to react and died one hour after completion of the operation. This death was reviewed in staff conference and was considered to have been preventable in that shock was not adequately treated before operation and that replacement of blood loss was insufficient.

Summary

Review of this series of cases of premature separation of the placenta will, we believe, establish the following principles concerning this complication:

1. Since toxemia of pregnancy is thought to be a potent etiological factor in approximately one-half of such cases, good prenatal care offers much in the way of prevention of abruptio.

2. No patient with hypertension should be allowed to be far from expert obstetric care.

3. Early recognition by both patient and physician, of the significance of antepartum hemorrhage is imperative.

4. In a decision to delay interruption of pregnancy in toxemia patients until the time of greater viability of the child, consideration must be given to the possibility of premature separation.

5. If the case be one of mild degree, the conduct of labor may be unaltered except for increased vigilance on the part of the attendant.

6. In the more severe cases the best interests of both mother and baby are served by as prompt evacuation of the uterus as is compatible with safety.

7. Manual dilatation of the cervix and other traumatic procedures for delivery have no place in the elective treatment of abruptio.

8. Treatment for shock and replacement of blood before instituting measures for delivery will greatly decrease the operative risk.

9. Prompt replacement of blood following delivery decreases not only the immediate danger, but also lessens the incidence of puerperal infection.

Placenta Previa

The second section of this presentation consists of a study of our experience with cases of placenta previa at the Philadelphia Lying-in Hospital from 1934 to 1945. We have included in this survey only those cases occurring beyond

the twenty-eighth week of pregnancy in which the diagnosis was definitely established by feeling the placenta through the cervix, its visualization by x-ray studies, or by confirming its low attachment at the time of cesarean section. By observance of these strict criteria, a large number of cases of mild painless bleeding were eliminated, even though it is quite likely that a relatively low implantation of the placenta existed in many of these cases.

TABLE XI. INCIDENCE OF PLACENTA PREVIA; PHILADELPHIA LYING-IN HOSPITAL 1934-45 (INCLUSIVE)

Total number of deliveries	28,288
Number of cases of placenta previa	92
Incidence of placenta previa	1 in 307

TABLE XII. TYPES OF PLACENTA PREVIA

	NUMBER
Lateral	25
Marginal	33
Central	20
Not stated	14
Total	92

As seen in the foregoing table the marginal type, in which the placenta covered only a portion of the internal os, was most frequently encountered. Next in order of frequency were lateral and central implantations.

TABLE XIII. METHODS OF DELIVERY IN PLACENTA PREVIA

		CASES	PER CENT
Vaginal delivery		17	19
Forceps	5		
Spontaneous	6		
Version and extraction	3		
Breech extraction	2		
Braxton-Hicks version	1		
Cesarean section		75	81

The choice of treatment in placenta previa is dependent upon the following factors: the severity of hemorrhage, the degree of shock, the location of the placenta, the viability of the child, its presentation; and, most important of all, the amount of cervical dilatation.

If the bleeding occurs during labor, and the placenta is marginal or lateral, and the presentation is polar, rupture of the membranes will most often allow the presenting part to make sufficient pressure on the separated placenta to control the bleeding. In such instances we allow labor to proceed to spontaneous delivery or to a low forceps application. If the cervix is completely dilated and if the baby is small, version and extraction may occasionally be the procedure of choice, except in the central type of implantation. Because of the potent danger of deep laceration of the cervix extending into the placental site, we feel that the manual dilatation of the cervix is strictly contraindicated.

Braxton-Hicks version, while occasionally a lifesaving measure for the mother under emergency conditions, is, we believe, best reserved for those cases of marginal and lateral placenta previa in which the child is dead or not viable.

By following these principles, we were able to deliver seventeen of our patients by the vaginal route, with no maternal mortality.

In seventy-five of our cases, cesarean section was performed. If the bleeding is profuse and the cervix is closed, we feel that the interests of both mother and child are best served by this procedure. Regardless of the amount of cervical dilatation cesarean section is done in practically every case of central placenta previa and in most instances of malpresentation.

TABLE XIV. MATERNAL MORTALITY FROM PLACENTA PREVIA; 1934-1945

Number of cases of placenta previa	92	
Number of maternal deaths from placenta previa	2	(2.2%)

TABLE XV. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY; 1934-1945
(PLACENTA PREVIA)

		PER CENT OF MORTALITY
Vaginal delivery	0 deaths in 17 cases	0.0
Cesarean section	2 deaths in 75 cases	2.7
Total maternal mortality	2 deaths in 92 cases	2.2

As seen in the above table, there were no deaths among the seventeen patients in whom the amount of cervical dilatation and other favorable factors permitted vaginal delivery. Unfortunately, a relatively small number were found amenable to such simple measures.

Following are the summaries of the two fatal cases of placenta previa:

CASE 1.—Cesarean section was done for central placenta previa under gas, oxygen, ether anesthesia. Bleeding was not profuse. The patient was obese (232 pounds), and was not in shock. She died of bronchopneumonia on the fifth postoperative day. The baby lived. This death was considered nonpreventable in our staff conference.

CASE 2.—The patient, with history of slight painless bleeding for six weeks, had a medical induction of labor, including three minims of pitocin. She immediately began to bleed steadily but not profusely. Cesarean section was done because of marginal placenta previa with only two fingers dilatation of the cervix. Profuse hemorrhage occurred during anesthesia. The baby lived. The mother failed to react to infusion during, and transfusion after operation. She died of shock and hemorrhage one and one-half hours later. This case was considered preventable in our staff conference in that shock was not adequately treated, a sufficient amount of blood was not given, and pitocin was used in the induction of labor.

TABLE XVI. GROSS FETAL MORTALITY ACCORDING TO METHOD OF DELIVERY
(PLACENTA PREVIA)

		PER CENT OF MORTALITY
Vaginal delivery	9 deaths in 17 cases	53
Cesarean section	15 deaths in 75 cases	20
Total fetal mortality	24 deaths in 92 cases	26
(Nine of the 24 dead babies weighed under 4 pounds)		
Corrected fetal mortality		18.5

Intrauterine asphyxia was presumably responsible for eleven fetal deaths and was, no doubt, a contributory cause in all of them. Prematurity was the next most frequent factor, as nine of the twenty-four babies who died weighed less than 4 pounds.

Our experience has resulted in our adoption of certain principles in the management of placenta previa.

1. Accurate diagnosis of the cause of bleeding is essential. A cautiously performed vaginal examination may reveal that the bleeding is due to a cervical polyp, an erosion, or, rarely, a cervical carcinoma, rather than to a placenta previa. Examination, however, entails the danger of sudden profuse bleeding as well as the risk of infection. It is our invariable rule that no patient suspected of placenta previa be examined until the operating room is ready for both vaginal and abdominal delivery.

X-ray studies by the "soft tissue" technique have in the past few years been a valuable aid in localization of the placenta. By this method the normally situated placenta is well visualized in practically all cases; the low-lying placenta is hidden by the pelvic bones. Finding the placenta high in the uterus is definite evidence against placenta previa; failure to visualize it indicates that the placenta is probably, but not necessarily, located in the lower uterine segment. The technique is, therefore, dependable only in ruling out, rather than positively diagnosing, placenta previa. This method of study is applicable obviously only to those patients whose bleeding has almost or entirely ceased. Our experience with the cystogram technique of Ude and Urner has led us to doubt its clinical value.

2. Treatment of shock and replacement of blood by transfusions of whole blood or plasma are essential before instituting procedures for delivery. Indeed, the patient should not be examined until she has reacted, because of the danger of additional hemorrhage from digital dislodgement of the placenta.

3. Expectant treatment of patients with placenta previa in the hope of bringing the child to greater viability is never justified unless the patient remains in the hospital throughout the remainder of pregnancy.

4. The method of delivery is almost wholly dependent on the status of the cervix. Because of the danger of profuse hemorrhage from the vessels of the placental site and the added risk of infection, manual dilatation of the cervix and forcible vaginal delivery have no place in the treatment of this condition. If the cervix is dilated and the placenta previa is only partial or marginal, rupture of the membranes will allow the presenting part to make pressure on the placenta sufficient to stop the hemorrhage. Under similar conditions version and extraction are indicated only if the cervix is *completely* dilated. Braxton-Hicks version, we feel, should be utilized only in those cases in which the baby is dead or nonviable and in which the cervix is partially dilated. While it is undoubtedly a valuable means of saving maternal life under emergency conditions, it entails almost certain sacrifice of the child.

The hydrostatic bag possibly has its place in the treatment of certain cases of marginal and lateral placenta previa but several instances of continuing intrauterine hemorrhage following its insertion have resulted in our abandonment of this procedure.

In all cases in which the cervix is not dilated, in all cases of central placenta previa regardless of the cervical dilatation, and in those of malpresentation

of the fetus. cesarean section is the safest, and therefore the most conservative form of treatment.

5. The use of an oxytocic intravenously immediately on completion of the second stage of labor, and firm packing of the uterus and the vagina after expulsion or removal of the placenta will considerably lessen the danger of post-partum hemorrhage. In most instances packing the uterus after cesarean section for placenta previa is advisable.

6. Blood transfusions are indicated following delivery to combat anemia and to improve the patient's resistance to infection.

Summary

1. A series of 113 cases of premature separation of the placenta is reported, with a maternal mortality rate of 1.8 per cent.

2. A series of 92 cases of placenta previa is reported, with a maternal mortality rate of 2.2 per cent.

3. Methods of management of these two complications are discussed.

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THE ELECTIVE USE OF KIELLAND FORCEPS IN MANAGEMENT OF OCCIPITOPOSTERIOR AND OCCIPITOTRANSVERSE POSITIONS

LEE M. MILES, M.D., F.A.C.S., ALBUQUERQUE, N. MEX.

(From the Department of Obstetrics and Gynecology of the Lovelace Clinic)

MANAGEMENT of labor in occipitoposterior and transverse positions of the fetal head has been in a static stage for many decades. The utmost of conservatism still prevails in the teaching and in the literature dealing with this subject. Whether the writer favors manual rotation to an anterior position with subsequent delivery with conventional forceps as advocated by Danforth¹⁻²; rotation of the head by "key in lock" multiple application of forceps; or some modification of the Seanzoni maneuver (Danforth³); or the use of Barton forceps (Langman and Taylor⁴); or the Kielland forceps (Kushner and Wahrsinger⁵); all agree that before any attempt to terminate labor full dilatation of the cervix with strong labor pains should have occurred for two hours or more, or that there shall be obvious signs of either fetal or maternal distress or both.

In this presentation I offer a critical analysis of 2,601 consecutive deliveries of private patients in which Kielland forceps were used in 547 instances of occipitoposterior and transverse positions. In the great majority of these 547 instances the forceps were used as an elective procedure to rotate and deliver the fetal head as soon as, or shortly after, full dilatation was obtained.

Occipitoposterior and transverse positions of the fetal head occur frequently, according to Bacon,⁹ 30 per cent of all vertex presentations; Danforth,¹⁻² 26 per cent; and Calkins,²¹ 48.3 per cent. Spontaneous rotation to an anterior position does occur frequently depending on a number of factors, the size of the fetal head and the size of the pelvis, the length of time allowed for molding of the head, the strength of the forces of labor and the internal contour of the pelvic passage. Much light has been shed on this last factor by the work of Caldwell and Moloy⁶ and Caldwell, Moloy, and D'Esopo⁷⁻⁸ in describing by means of extensive x-ray studies the type of pelvis in which posterior and transverse positions are likely to persist.

Kielland Forceps

American medical literature is not replete with articles pertaining to the use of Kielland forceps. Although Kielland presented his forceps and described in detail his method of using the instruments in 1915, it was not until 1924 that Greenhill¹⁰ made a thorough study of collected reports from European literature. Since then sporadic articles have appeared in American medical journals.¹¹⁻¹² Most of these articles are brief accounts of the use of Kielland forceps in a small series of cases. Kushner and Wahrsinger⁵ and Langman and Taylor⁴ presented excellent statistical studies of significantly large series of cases.

Lengthy descriptions of the forceps themselves and the method of their use are not necessary. There are, however, a few points that will bear emphasis.

With two exceptions, the instruments should always be applied in the original Kielland manner. This consists in first introducing the anterior blade well into the uterine cavity, and then rotating it into apposition with the fetal head. This rotation should cause the tip of the blade to describe an arc in a "clockwise" direction when the occiput is directed to the right side of the mother's pelvis, and "counter clockwise" when left occipitoposterior or transverse position of the head is present. In actual use two fingers of the left hand are inserted into the vagina and between the cervix and the fetal head. The head should not be disengaged or disturbed in any manner. The tip of the anterior blade, pointing upward, is then inserted between the fingers in the vagina and the cervix. Frequently as the blade passes into the uterine cavity there is encountered a definite resistance. If the examining fingers are thrust upward this resistance is found to be due to a constriction of the uterine muscle at the level of the junction of the cervix with the uterine musculature. Johnson²⁰ has described this condition and calls it "temporary or functional contraction ring." If delivery is too long delayed, this "functional" contraction ring may become the pathologic contraction ring. When this resistance is encountered the handle of the forceps is elevated and the tip of the blade passes readily into the uterine cavity, where it can be rotated and applied to the fetal head. The posterior blade is then inserted and articulated with the anterior blade.

The two exceptions to this method of insertion of the blade are: first, when a true contraction ring is present it is dangerous to attempt the insertion of the blades by the rotation method and in this case the "wandering" manner of insertion is advisable; second, when the head is low in the pelvis and the occiput is directly posterior the blades are applied to the sides of the fetal head exactly as with classical forceps, keeping the markers on the handles directed toward the occiput. The head may then be rotated without difficulty and delivered with a single application of the forceps.

Rotation of the head may be accomplished by one of three procedures:

1. *Rotation without traction.* If the head is lying in the plane of greatest pelvic diameter, gentle rotation of the handles in a straight line and not with a sweeping movement, will usually suffice to bring the occiput to an anterior position.

2. *Rotation with traction.* If the method described above does not readily produce rotation, traction with rotation simultaneously applied will produce rotation accompanied by descent of the head.

3. *Disengagement of the head with rotation above the pelvic brim.* This would appear to be a dangerous and radical procedure. However, the cephalic curve of Kielland forceps fits the fetal head so accurately that thrusting the head up and out of the pelvis does disengage the head from the forceps. The head is readily rotated to an obliquely anterior position and traction with the resulting descent of the head and further rotation brings the head to the desired anterior position and delivery is effected.

It is, of course, understood that there is no cephalopelvic disproportion existing that precludes the possibility of delivery through the vagina. Traction for delivery should be applied in the direction naturally taken by the handles

of the forceps. Too early elevation of the handles causes deflexion of the head with the result that too great force is necessary to bring about delivery and the more unfavorable diameter of the head as it is forced through the birth canal may result in severe lacerations of the outlet.

Material

The material for this analysis consists of 2,588 consecutive private patients delivered at St. Joseph's Hospital and at the Southwestern Presbyterian Hospital. Neither of these hospitals has an intern or resident staff. Labors and deliveries were conducted by myself with the assistance of a very efficient nursing staff. In order to have the results uniform and not subject to personal variation, the work of my associates is not included in this report. With necessary variations to suit individual cases, a definite routine as regards nutrition, elimination, observation and medication was carried out in all cases. All labors were conducted by vaginal examinations preceded in each instance by a vaginal instillation of 15 c.c. of a 5 per cent aqueous solution of Mercurochrome. In this series 2,588 mothers were delivered of 2,601 babies, twins having occurred twenty-six times.] Table I shows the distribution of these cases by presentation of the fetus.

TABLE I

PRESENTING PART	NUMBER	PER CENT
Vertex	2,499	96.07
Breech	93	3.60
Shoulder	7	.26
Face	2	.07
Total	2,601	100.00

Table II breaks down these figures still further to show the method of delivery.

TABLE II

TYPE OF DELIVERY	NUMBER	PER CENT
Breech	93	3.60
Version and extraction	26	1.00
Cesarean section	78	2.99
Decapitation	1	.038
Craniotomy (hydrocephalus)	1	.038
Occipitoanterior (spontaneous or outlet forceps)	1,808	69.51
Occipitoposterior (Scanzoni or key in lock)	7	.26
Occipitoposterior (manual rotation)	9	.346
Occipitoposterior (delivered as such)	31	1.19
Occipitoposterior (Kielland forceps rotation)	547	21.03
Total	2,601	100.00

These 547 cases in which Kielland forceps were used for rotation and delivery of fetuses presenting in occipitoposterior position were comprised of two groups of patients. Thirty-six of these patients were referred to me for delivery after attempts at delivery, including attempts at forceps delivery, version and full doses of pituitrin, had failed. Some of these women had traveled long distances, one came over 200 miles. These women all presented the classical findings referred to as the customary indications for operative intervention. These

patients had all been in labor for hours without progress, the mothers were in a state of near exhaustion, the fetal heads were all extremely molded, and the fetuses were all in evident distress if not already dead. This group contributed largely to the number of morbid mothers and to stillborn infants and to neonatal deaths.

The remaining 511 cases consisted of mothers who were under my care from early in pregnancy through labor. In this group of patients I did not set any arbitrary time limit before which operative assistance* was contraindicated, such as two or more hours of hard second stage labor, nor did I wait for signs of maternal or fetal distress or both. When the cervix was fully dilated and the head deeply engaged in the pelvis, the patient was taken to the delivery room and prepared for delivery. Under anesthesia the Kielland forceps were applied in the original manner and the head rotated and delivery effected. I do not consider it to be necessary or advisable to remove the Kielland forceps and apply conventional instruments for the actual delivery.

Maternal End Results

Such a radical departure from the conventional indications for any procedure to assist rotation and delivery of the fetus presenting in occipitoposterior or occipitotransverse positions must be justified by the results obtained. The results are presented in Table III, showing the effect of the procedure from the maternal standpoint. The standard of morbidity used in this series is that established by the American College of Surgeons. There were no deaths from infection in the entire series. Of the patients delivered by Kielland forceps who had a febrile puerperium, seven were among those patients who were brought to the hospital after long labor and attempts at delivery made at home under anything but proper conditions. All seven had intrapartum infection before arrival at the hospital.

TABLE III

Total mothers delivered	2,588	
Total morbidity	95	3.67%
Mothers delivered other than by Kielland forceps	2,041	
Morbidity	76	3.72%
Mothers delivered by Kielland forceps	547	
Morbidity	19	3.47%

Actual causes of morbidity of the entire group were as follows: acute pyelocystitis, thirteen; acute respiratory tract infection, five; active pulmonary tuberculosis, two. All the remaining febrile reactions were considered to be puerperal in origin. There were three cases of thrombophlebitis in the entire series. *No prophylactic administration of sulfonamides or penicillin was used.* These drugs were administered on indication only and the sulfonamides were used in exactly fifty instances, and penicillin in only six cases. Total maternity mortality in the 2,588 mothers was six. In the series of 547 mothers delivered by Kielland forceps there were two deaths, neither death could be attributed to the method of delivery. One death occurred in the case of an eclamptic woman who was brought to the hospital comatose and moribund, and the other death was due to a pulmonary embolus.

Other maternal complications in this series were postpartum hemorrhage and lacerations or extensions of episiotomy incisions involving the rectum. Postpartum hemorrhage occurred in the group of 547 women delivered by Kielland forceps in six cases, or 1.09 per cent, and among the 2,041 women delivered by other means the occurrence of hemorrhage was twenty-two, or 1.07 per cent. The only complication that occurred with greater frequency in those mothers deliv-

*The terms "operative interference" and "operative intervention" should be deleted from obstetric terminology and the term "operative assistance" substituted.

ered by Kielland forceps than in the other group was laceration involving the rectum, five cases in the Kielland forceps group, and two cases in the mothers delivered by other means. In only one instance did the laceration include the sphincter muscle, the others were lacerations into the lumen of the bowel above the sphincter muscle. All were treated by immediate repair and all healed without complication. The one complete tear followed use of conventional forceps. On discharge from the hospital, and at the postpartum examination, her sphincter control was good.

From the above analysis it is evident that, as far as the mother is concerned, there is no appreciable difference in the outcome of delivery as the result of the elective use of Kielland forceps as compared with the other methods of delivery.

Fetal End Results

The object of all obstetric care is to complete the cycle of pregnancy, parturition, and puerperium with a well mother and a well baby. Table IV analyzes the results from the standpoint of fetal survival.

TABLE IV

Total births other than by Kielland forceps	2,054	
Stillbirths under 1,500 Gm.	10	0.48%
Stillbirths over 1,500 Gm.	33	1.6 %
Neonatal deaths under 1,500 Gm.	22	1.07%
Neonatal deaths over 1,500 Gm.	16	0.78%
Total births by Kielland forceps	547	
Stillbirths over 1,500 Gm.	5	0.9 %
Neonatal deaths over 1,500 Gm.	8	1.46%

Among the babies delivered by Kielland forceps there were no fetuses under 1,500 Gm. in weight. Of the five stillborn fetuses, four were badly macerated at birth. Of the eight neonatal deaths among the fetuses delivered by Kielland forceps, autopsy demonstrated three cases of anatomical conditions incompatible with life: pulmonary atelectasis one, congenital cystic kidney one, hydrocephalus and spina bifida one. Excluding these three cases of congenital deformity, the corrected neonatal mortality is 0.90 per cent. Of the five remaining neonatal deaths only one autopsy was obtained, and that showed the cause of death to be intraeranian hemorrhage, and the same cause was ascribed to the other four deaths. These deaths occurred in the group of cases that would be usually classified as "indicated" Kielland forceps deliveries. In the group of fetuses delivered by the "elective" use of Kielland forceps such fetal complications as marked molding of the fetal head, caput succedaneum and cephalhematoma were almost entirely absent.

There were only six instances in which delivery could not be effected by Kielland forceps. In these six cases the forceps were successfully applied and rotation was accomplished, but traction did not result in descent of the head and the forceps were removed. Cesarean section was performed twice with good results to mother and baby, version was done four times, with good result in three. In the fourth case, not considered as safe to perform a section, the version delivery resulted in fetal injury which developed into hydrocephalus of traumatic origin and the child died at the age of 2 years.

Discussion

It is now a matter of general agreement that, as far as the mother is concerned, the skillful use of forceps under suitable conditions to effect delivery, does not affect the outcome so far as life and health are concerned. From the

maternal viewpoint, the end result of the use of forceps is that labor is shortened. In spite of a great variety of procedures aimed at decreasing the pain of childbirth, ranging from mental suggestion to continuous caudal anesthesia; in spite of a great variety of analgesic drugs, the fact remains that the *one positive thing* we can do to lessen the pain and shorten the period of suffering is to give the parturient woman the benefit of operative assistance in delivery. Is this worth while? The late Dr. Joseph B. DeLee thought it was when he advocated the routine use of forceps in the procedure for which he coined the name *Prophylactic Forceps*.

In the case of occipitoposterior positions, it is well recognized that the first stage of labor is prolonged. Not only is the first stage prolonged, but the particular character of the pains is more severe than in occipitoanterior positions. This is probably due to the fact that in most occipitoposterior positions, the cervix lies far posterior in the hollow of the sacrum and the uneven pressure on the cervix is peculiarly painful. I have shown in this series of cases in which Kielland forceps were used early in the second stage, that the procedure is devoid of danger to the mother. Kushner and Wahrsinger⁵ state, "There were six cases of mitral stenosis, where the second stage was entirely eliminated. Forceps (Kielland) were applied when full dilatation was attained." If, as I have demonstrated in my study of 547 cases of the use of Kielland forceps, and as the writers quoted above admit, the early application of Kielland forceps in occipitoposterior and transverse positions is safe for the mother, and results in shortening her labor and relief of pain, it is therefore a worth-while procedure.

From the standpoint of the fetus which has had the misfortune to present itself in an occipitoposterior position, the matter of early versus late application of Kielland forceps with rotation and delivery is a matter of vital importance. Langman and Taylor⁴ report 134 instances of their use of Kielland forceps with fetal and neonatal loss of twenty-one. Kushner and Wahrsinger⁵ report 200 cases with a fetal and neonatal loss of fourteen. In my series of 547 deliveries with Kielland forceps, the fetal and neonatal loss was thirteen. It is not my purpose to compare my skill in the art of Kielland forceps application with these other writers. It is my intention to point out that the essential difference in results is directly due to early delivery before damage has been done to the fetus as the direct result of the forces of labor. In none of my cases was an arbitrary "watching and waiting" time required. In the great majority of my own cases, forceps were applied shortly after full dilatation was attained. The disastrous results to the fetus in my series were due to delay. It is my firm conviction that had delivery been effected earlier in labor in all instances, the fetal loss would have approached zero.

Summary and Conclusions

1. A critical study of 547 deliveries with Kielland forceps out of a total of 2,601 consecutive deliveries is presented.

2. Maternal morbidity and maternal complications were not increased by the procedure of early application of Kielland forceps.

3: Two maternal deaths occurred in this series of 547 deliveries, neither of which could be attributed to the method employed in delivery.

4. The total fetal loss was thirteen—net loss ten.

5. The best results from the fetal standpoint were in those instances in which Kielland forceps were applied early in the second stage of labor.

6. The early application of Kielland forceps is accomplished with less difficulty and with much less occurrence of damage to either mother or baby than the application late in the second stage of labor.

7. Kielland forceps are ideal for dealing with occipitoposterior and transverse positions.

8. The use of Kielland forceps under suitable conditions as an elective procedure is recommended in dealing with these cases.

My appreciation is tendered to Sister Williamana, Medical Librarian of St. Joseph's Hospital, and to Miss Lillian Henningson, Medical Librarian of the Southwestern Presbyterian Hospital, for their assistance in making these records available for study.

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A MULTIPLE SULFONAMIDE THERAPEUTIC MEASURE IN THE POSTOPERATIVE CARE OF THE CERVIX AND VAGINA*

A. HERBERT MARBACH, M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Jewish Hospital)

IN RECENT years the knowledge of vaginal physiology¹⁻⁹ has increased tremendously. In diseased states of these organs we attempt to redirect pathologic variables to a state of normal physiologic function, with judicious expedition, through the utilization of chemotherapeutic principles. Medicine's recent advances in chemotherapy have been remarkable. With these newly applied principles, the healing times in vaginal and cervical operations can be decreased considerably.

In postoperative vaginal and cervical conditions there exist four main physiologic imbalances tending to delay prompt healing:

1. The patient's vaginal flora changes, from Grade 1 to Grades 2 and/or Grade 3.

2. The pH approaches neutrality.¹⁰⁻¹³ There is a progressive swing of the pH toward that favoring the more optimal growth of secondary bacterial invaders.

3. The epithelial strata are destroyed or decreased in height. This is related to catabolic excretions of low grade pathogenic bacteria hostile to superficial mucosal cells by virtue of exotoxins and other unfavorable excretory substrates.

4. The glycogen availability of the tissue is decreased. As the upper mucosal layers, containing the greater amount of this polysaccharide, are destroyed the glycophilic needs of the secondary bacterial invaders become more adequate. A vicious circle is thus developed. Too, we are aware the acidosis of anesthetics exert a direct glycogenolytic influence upon the body tissues.²⁴ All these depriving variables contribute to the continuing depletion of normal glycogen content.

One logical approach to decrease the vaginal discharge and restore normal physiological mucosal balance was to suppress the secondary bacterial invaders. It is principally these saprophytic invaders which are responsible for the changes in the delicate physiologic equalization.

The role of the sulfonamide derivatives was considered to represent one possible approach toward the assistance of the normal reparative process, provided the formulation of such therapy considered such additional requisites to tissue repair than only the control of bacterial invaders. It is known that sulfonamide derivatives control secondary bacterial invaders at optimally specific bacteriostatic ranges. Cowles¹⁴ demonstrated that the maximal bacteriostatic action for a given sulfonamide half dissociation constant was obtained within its paralleling specific pH range. A further indication for the

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use of more than one sulfonamide is found in Lehr's¹⁵ studies of inhibition of drug precipitation in the urinary tract by sulfonamide mixtures. It was possible to obtain such a mixture of sulfa derivatives whose optimal pKa's and parallel pH's would fall within the maximal and minimal pH range encountered during the course of healing of cervicovaginal operative lesions. This hypothesis was subjected to a carefully controlled laboratory study prior to initiation of the present clinical study.

The enhancement of sulfonamide activity by urea and related compounds has been demonstrated by several investigators.¹⁶⁻²⁰ This action depends on the facts that (a) bacteria, especially Gram-negative organisms, are killed or inhibited by urethane and carbamates themselves; (b) urethanes and their derivatives have a competitive action on para-aminobenzoic acid which is inhibitory to sulfonamides.

The problem of application of these drugs to the surgical area was considered. In view of the wide but convoluted epithelium of the vaginal rugae to be covered, as well as the irregular crevices and interstices occasioned by operative procedure, it was necessary to select a base which would adhere to the mucosal surfaces as well as be water-dispersible and absorptive in nature.²¹ The dosages of sulfa derivatives was determined upon a molecular equivalent basis that no more than 10 per cent of the formula were sulfa crystals by weight. This percentage of the actual principles was distributed as follows: 3.42 per cent sulfathiazole, 2.86 per cent acetyl-sulfanilamide, 3.70 per cent benzoyl-sulfanilamide and 1 per cent urea peroxide.* Animal studies revealed non-toxicity and no untoward side effects. Absorption rates through intact and disrupted mucosal surfaces were performed. Rabbits weighing approximately 4.0 kg. were used in the study. Three grams of cream were applied over a shaved area upon the dorsum. Hourly blood levels were determined. The peak of absorption, at the fourth hour, was 2.50 mg. per cent in the median instance. The value never exceeded 4.0 mg. per cent in any case. Absorption of the topically applied multiple sulfa cream was rapid, reaching a peak within four hours and disappearing almost entirely from the blood within twenty-four hours. The blood concentration of the total sulfonamides was below usual sulfonamide values, rising to less than 3 mg. per 100 c.c. of whole blood at any time.

Blood levels in rabbits were determined similarly after vaginal application of 3.0 Gm. of cream. The peak blood level, at five hours, was found to be 1.87 mg. per cent or 0.35 per cent per kg. body weight. The first 25 humans in this series whose blood sulfa concentrations were determined yielded only traces, several determinations rising between 0.2 to 0.4 mg. per cent. It was obvious, therefore, that the preponderant sulfonamide activity was available to the mucosal surfaces in immediate contact.

Controlled tissue tolerance tests were carried out on albino female rats. The animals were sacrificed at varying times and histologic sections of the vagina, cervix, kidneys, and liver revealed no abnormal changes. Allergic and

*The multiple sulfa cream used in this study was the Triple Sulfa Cream prepared and furnished by the Ortho Research Foundation, Raritan, New Jersey.

sensitization sulfonamide studies were determined by testing twenty-three human subjects with patch tests. No sensitivity was observed in any instance, again indicating major sulfa activity at site of application rather than systemic in action.

In Vitro Bacteriology Evaluations

Bacteriologic tests in vitro were then carried out, using the agar cup procedure. Two-tenths of a cubic centimeter of an eighteen-hour broth culture of *Staphylococcus aureus* was inoculated into approximately 20 c.c. of heart infusion agar adjusted to pH 4.6, 5.2 and 7.0. The multiple sulfa cream preparation was enclosed in a glass ring of 1.5 cm. in diameter and placed on top of the solidified inoculated agar. The plates were then incubated for twenty-four hours at 37° C. The zone of inhibited growth was measured in mm. as follows:

at pH 4.6 —11 mm. zone
pH 5.2 —11 mm. zone
pH 7.04—12 mm. zone

The results obtained in these experiments, as a whole, exhibited consistently clear-cut zones of bacteriostasis at the specific pH levels.

In view of our desire to evaluate multiple active sulfonamide principles upon postoperative sites, it was deemed advisable to determine the sterility of the preparation itself. The following method was used: one-tenth gram samples were taken aseptically from a portion of a tube near the orifice and again at a point approximately halfway down the tube. These amounts of the sulfa cream were placed in duplicate tubes of thioglycollate culture medium containing three different amounts of para-aminobenzoic acid. The amounts of P.A.B.A. were so adjusted in the three series that the ratio of sulfonamide to P.A.B.A. were 10/1, 100/1, 1000/1. The thioglycollate medium provided optimal culture conditions for both aerobes and anaerobes. After seventy-two hours incubation at 37° C. subcultures were made into homologous thioglycollate medium containing the same amounts of P.A.B.A. After a second incubation period of seventy-two hours, the subcultures were observed for evidence of gross bacterial populations, and the clear tubes were recorded as containing no live bacteria. All negative tubes were incubated nine days before final judgment was made. These negative tubes were then inoculated with *Candida albicans* and *Clostridium sporogenes* to determine whether or not either a pathogenic fungus or an anaerobe, if present in the original multiple sulfa cream, would have grown in the test culture medium. In addition, at the time the original test was set up, control tubes of thioglycollate medium containing the same amounts of P.A.B.A. were inoculated also with *Staphylococcus aureus*.

Duplicate samples from eight different batches of cream were tested. None were found to contain live bacteria or spores detectable by the method described above. All control tubes developed high bacterial populations and all of the negative tubes which were inoculated with *Candida albicans* and *Clostridium sporogenes* likewise supported good bacterial and fungus growth, demonstrating the validity of the test method. It was therefore concluded that the multiply-derived sulfa cream was sterile as prepared pharmaceutically.

The antiseptic action of the cream was investigated in order to gain information regarding its in vitro action against a variety of organisms which might be encountered in wound infections. The following bacteria were used: *Bacillus anthracis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus vaginalis*, *Streptococcus hemolyticus*, Group A: *Streptococcus hemolyticus*, Group D: *Escherichia coli*, *Clostridium tetani*, *Clostridium perfringens* and *Pseudomonas aeruginosa*. One cubic centimeter of the specially developed sulfa cream was seeded with 0.1 c.c. of a twenty-four or forty-eight hour culture of the test

organism and stirred with a sterile glass mixer for two minutes. Subcultures were then made into thioglycollate medium containing the three above-mentioned concentrations of P.A.B.A. at five, ten, fifteen, thirty, and sixty minutes, and twenty-four hours. The subcultures were incubated for seven days. Gram-stained smears were prepared from the tubes at the critical exposure times, to make certain that the bacteria found were those used in the inoculum. All negative subcultures were again subcultured into thioglycollate broth and observed an additional seven days. All tests were run in duplicate. Two types of controls were set up: (a) the test organisms were inoculated directly into media containing three concentrations of P.A.B.A.; (b) the multiple sulfa cream direct from tubes was inoculated in the same medium in order to further check its original sterility.

The results of these tests are shown in the following table:

TABLE I. THE ANTISEPTIC ACTION OF A MULTIPLE SULFA CREAM

TEST ORGANISM	KILLING TIME
<i>Bacillus anthracis</i>	5 min.
<i>Pseudomonas aeruginosa</i>	5 min.
<i>Bacillus subtilis</i>	5 min.
<i>Streptococcus vaginalis</i> (hemolytic)	5 min.
<i>Staphylococcus aureus</i>	30 min.
<i>Escherichia coli</i>	60 min.
<i>Clostridium perfringens</i>	30-60 min.
<i>Clostridium tetani</i>	60 min.
<i>Streptococcus hemolyticus, A</i>	1-18 hr.
<i>Streptococcus hemolyticus, D</i>	1-18 hr.

All control cultures gave luxuriant growth. No evidence of bacterial growth was observed in tubes receiving the cream alone.

It was concluded that the cream destroys a wide variety of pathogenic organisms of the types commonly found in surgical wounds. The killing time in all cases was brief enough to insure the destruction of these organisms during the period of time in which a special sulfa cream would be expected to remain on the wound site.

With this experimental background, and a working hypothesis of goals we hoped to attain physiologically and therapeutically, we initiated clinical evaluations on postoperative patients in whom the mucosal continuity of some area of the lower genital tract had been broken. Our previous experience with such cases was that for a period of five to six weeks following conization, vaginal hysterectomy, and vaginal plastic operations there existed vaginal discharge, greenish-brown to yellowish-green in color, malodorous in some, and moderately profuse in amount. Upon inspection of the operative sites, particularly those involving the cervix uteri, a gray-green membrane covered the areas, appearing about the fourth day and loosening on the sixteenth to the twentieth day. This membrane was unaltered by the local application of the usual aqueous or alcoholic antiseptics, even though hydrogen peroxide had been used as a prior cleansing agent. When these factors were considered, i.e., the prolongation of healing time, localization of a slough, and the annoying discomfort and embarrassment to the patient requiring added necessity for frequent douches, the multiple sulfa cream preparation was tried. Two hundred cases were studied including 121 conizations of the cervix and 79 vaginal plastic operations.

Discussion

Within twenty-four hours after operation, or upon the removal of vaginal packs or cervical wicks, approximately 5.0 Gm. of multiple sulfa cream was

inserted into the vaginal canal twice daily. The patients were examined twice weekly following the seventh postoperative day. At the time of each office visit the patients were questioned as to the odor, number of napkins used to control leucorrheal discharge, and localized pelvic discomfort.

One of the most annoying symptoms, the malodorous discharge, was found nonexistent in all the treated cases. On speculum inspection, the operative site was red and appeared always as a clean granulating surface without a superficial membrane attached, and no apparent slough present.

It was noted in the conization series that at the tenth and eleventh days, epithelialization was in active progress as evidenced by the furred appearance at the advancing reparative edges of the vaginal portions of the coned canal. Healing was completed as early as the sixteenth postoperative day and as late as the twenty-fourth postoperative day in contrast to twenty-eight days²² to forty-two days.²³ See Table II illustrating these time factors.

TABLE II. OPERATIVE PROCEDURES.* TWO HUNDRED CASES TREATED WITH COMPOUND SULFA CREAM IN THE POSTOPERATIVE PERIOD

	NO. OF CASES	AVERAGE TIME OF HEALING
Anterior colporrhaphy	29	16 days
Perineorrhaphy	25	17 days
Colpocleisis	2	17 days
Cervical amputation	6	22 days
Third degree tear repair	2	11 days
Vaginal hysterectomy	15	18 days
Cervical conizations	121	20 days
	200	

*Several types of lower canal surgical procedures were performed upon single cases.

In 899 conization cases Miller and Todd²³ found an incidence of proved stenosis in 6.46 per cent with a probable incidence in an additional 2.51 per cent. In our series the cervical canals were sonided upon the 21st day in all conization cases and no occlusions were discovered. There was, however, a slight increase in the amount of granulation ooze noted during the second postoperative week, as compared to the amount seen previously in patients where slough was present in those who had not been treated with the multiple sulfa cream in the postoperative period. Before this treatment was instituted we noted an increase in the amount of bleeding at about the twenty-fifth day, which was then attributed to the detachment of the sloughing membrane covering the thrombosed and infarcted vessels. Since the same bleeding takes place with multiple sulfa therapy during the second postoperative week, and since this stage corresponds to the twenty-fifth day or thereabouts in the healing schedule without therapy, it may be the ooze is occasioned by the beginning of the epithelialization and onset of angiomatous proliferation. Histologic work on this subject is now in progress.

In this series of cases one patient developed a parametrial abscess which necessitated posterior colpotomy. The operative vaginal site, however, showed rapid healing. Following evacuation of the parametrial abscess, complete recovery ensued.

In the sixty-four vaginal plastic cases the same rapid healing time and decrease in discharge was noted. However, where complete epithelialization occurred earlier, the sutures remained in place even after thirty days, and in many cases the twenty-day catgut had to be removed much as any nonabsorbable suture material.

In these simple vaginal plastic procedures not involving cervical surgery, there was seldom any abnormal increase in vaginal discharge noted. In this group of cases the compound sulfa cream was used solely to decrease the bacterial flora. Of particular interest were two LeFort colpecteisis operations, done on women both past 70 years of age. In both instances the healing was prompt and complete. Needless to say, meticulous care was exercised in the introduction of the multiple sulfa cream along the lateral troughs.

Summary

In an attempt to enhance healing and obtain a corollary decrease in the postoperative vaginal discharges, a newly developed multiple sulfa cream was evaluated. Its component sulfonamides included sulfathiazole, N-acetyl-sulfanilamide, N-benzoyl-sulfanilamide in addition to urea peroxide. The three sulfa compounds were found useful in combatting the secondary bacterial invaders which grow more luxuriantly at the elevated and optimally pathogenic pH levels. The urea peroxide proved useful in improving the bacteriostatic and bacteriocidal action of the sulfonamide preparation itself. Urea peroxide is also bacteriocidal and does exert some debriding action upon the denuded mucosal surfaces.

Bacteriologic and histologic studies in vivo and in vitro were carried out to insure low toxicity of such topically applied multiple sulfa derivatives incorporated in an absorptive cream base.

Two hundred surgical patients have been carefully followed over a period of eighteen months and the clinical efficacy of the preparation was demonstrated.

Conclusions

1. A recently developed compound sulfa cream, embodying normal physiologic and chemotherapeutic principles, was studied and its efficacy in treating the postoperative cervix and vagina was demonstrated in 200 gynecologic cases.

2. The high bacteriostatic and bacteriocidal action of this multiple sulfa topical preparation, at the important pH ranges of 4.6, 5.2, and 7.0 was demonstrated clinically and in the laboratory. As the reparative processes of lower genital tract mucosa increased the elevated pH of the surface infected wounds regressed to normal hydrogen ion values ranging between pH of 4.0 to 5.0.

3. The compound sulfa cream is a sound addition to the postoperative period not only because of ease of administration and the fact that annoying vaginal discharges were decreased to a minimum but primarily because the healing time of such mucosal surfaces was reduced to 50 per cent of what it was previously as compared to control cases.

The author is indebted to Dr. Camille J. Stamm for his kindness in contributing his cases to this study; and to the Ortho Research Foundation for making available full experimental laboratory data.

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ANEMIAS OF PREGNANCY

PETER J. TALSO, M.D.,* AND WILLIAM J. DIECKMANN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of The University of Chicago and The Chicago Lying-in Hospital)

A DECREASE in the hemoglobin concentration, hematocrit, and erythrocyte count of the peripheral blood occurs during pregnancy. True anemia of pregnancy has been defined as a condition in which these constituents are reduced below the level considered physiologic for the period of gestation.¹ Various minimal hematologic standards for normal pregnancy have been proposed.^{1, 2, 3} For this study a hemoglobin of 10 Gm. per cent, a hematocrit of 33 per cent, and an erythrocyte count of 3.36 million per cubic millimeter were considered as the minimal normal values between the twelfth and the thirty-sixth week of pregnancy.²

Many observers have described satisfactory therapeutic results using iron preparations alone or in combination with other substances.^{1, 4, 5, 6, 7} Others have ascribed little efficacy to these agents.^{2, 8} In view of these discrepancies we feel that adequate comparison with simultaneously observed controls is lacking. As a result, this study was undertaken to review the cases of anemia of pregnancy followed at the Chicago Lying-in Hospital during the past several years.

Initial and periodic hemoglobin determinations are very important parts of prenatal and postpartum care. The usual methods for determining hemoglobin—either with the visual or photoelectric colorimeter—require very small amounts of blood, 0.02 ml. and dilutions of 100 to 400 times. Thus the combined error of the pipette and chamber, as well as the technician may be 7 to 15 per cent. The hematocrit and erythrocyte count are methods for determining the number of red blood cells per unit of blood. The hematocrit has a closer correlation with the hemoglobin concentration than the red cell count, because the error in the former is approximately 2 per cent, while the minimum error in the red cell count is over 8 per cent. For over ten years we have been using the hematocrit determination on heparinized blood as a screening method. Any patient who is less than twelve weeks pregnant or more than six weeks post partum whose hematocrit is less than 37 volumes per cent is referred to the antepartum anemia clinic. Between twelve weeks and thirty-six weeks gestation the lower limit of the hematocrit is 30, and between thirty-six weeks and term the lower limit is 32 volumes per cent. The procedure in the anemia clinic is to obtain additional history and special examinations as to possible causes for the anemia. A diet history is obtained in some instances. The hemoglobin,

*Present address: Medical Department Field Research Laboratory, Fort Knox, Kentucky.

hematocrit, red cell count, leucocyte count, and differential determinations are made. The various indices, mean corpuscular hemoglobin, and cell volume, etc., are determined and the anemia classified. For purposes of this study, all cases complicated by blood loss, toxemia, and infection were excluded.

After a preliminary observation period of two to six weeks during which the determinations were repeated, therapy was begun. All treated cases received iron in doses accepted to be adequate.⁹ Also, in certain of the cases accessory hematopoietic substances such as vitamins of the B complex, desiccated hog's stomach, and liver extract were administered in addition to the iron. In the graphs and tables these are included under the heading: Iron and Vitamins. After the institution of therapy the cases were followed at biweekly intervals until three to six months post partum with periodic blood studies. Patients with hemoglobin concentrations of six grams per cent or less were hospitalized for a more detailed study. In some cases transfusions of whole blood served as the principal therapy given or as a supplement to other treatment.

Results

Two hundred fifty cases were studied. These have been classified as to mean corpuscular volume⁹ and therapy administered (Table I). The mean corpuscular hemoglobin concentration⁹ was determined in each case, and it was found that 42 per cent were normochromic, 56 per cent hypochromic, and 2 per cent hyperchromic. At the time of their first visit 57 per cent of the entire group were anemic. This represented 61 per cent of the treated group and 48 per cent of the controls.

TABLE I

	NO. OF CASES	GAIN OF Hb IN GM. IN 21 DAYS				
		A	B	C	D	E
		DECREASED OR UN- CHANGED	0 TO 1.5 GM.	1.6 TO 3.3 GM.	OVER 3.3 GM.	MEAN GAIN GM.
Macrocytic						
Controls	12	5	5	1	1	$0.82 \pm .20^*$
Iron alone	31	10	15	6	0	$0.73 \pm .09$
Iron and vitamins	19	6	8	4	1	$0.92 \pm .15$
Transfused	2					
Subtotal	64					
Microcytic						
Controls	39	8	23	5	3	$0.86 \pm .09$
Iron alone	53	11	24	17	1	$1.24 \pm .09$
Iron and vitamins	32	9	13	8	2	$1.04 \pm .14$
Transfused	9					
Subtotal	133					
Normocytic						
Controls	25	13	11	1	0	0.24 ± 0.6
Iron alone	27	10	12	5	0	$0.73 \pm .12$
Transfused	1					
Subtotal	53					
Total	250					

*Probable error of mean.

⁹Iron was prescribed in the following daily doses: Ferrous sulfate, 1.0 Gm.; Ferric ammonium citrate, 5.0 Gm.; or Ferrous Carbonate, 5.0 Gm.

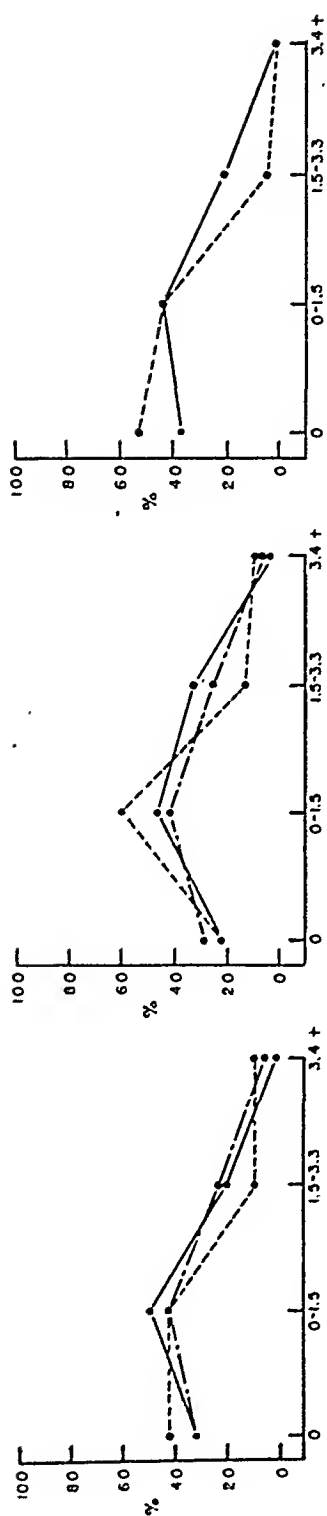


Fig. 1.

TABLE II

COMPARISON OF TREATED GROUP WITH CONTROLS AT BEGINNING OF OBSERVATION PERIOD				
	MEAN AGE	MEAN NO. OF PREG.	MEAN Hb	MEAN WEEK OF PREG- NANCY
Untreated controls	$28.3 \pm .5$	$3.2 \pm .2$	$9.1 \pm .09$	$31.4 \pm .4$
Treated group	$27.5 \pm .3$	$3.2 \pm .1$	$9.0 \pm .06$	$31.2 \pm .3$

TABLE III

	MACROCYTIC		MICROCYTIC		NORMOCYTIC	
	Hb	SD*	Hb	SD*	Hb	SD*
Controls	10.2	0.7	9.6	1.4	9.8	1.3
Treated group	11.1	1.4	10.6	1.9	11.3	1.7

*SD, Standard deviation.

During adequate therapy the expected rate of hemoglobin formation is 0.078 Gm. per day, and the maximum is reached between the second and fourth week.^{10, 11} For this reason a twenty-one-day observation period was selected in order to evaluate the effects of treatment. At the beginning of this period the treated group showed no significant differences from the controls (Table II).

The gain in hemoglobin concentration in the various groups during the three weeks of observation is recorded in Table I (Columns A to D). Inspection of these data reveals that the number of cases showing the expected gain in hemoglobin during this observation period, 1.6 Gm. in twenty-one days, is only slightly greater in the treated groups than in the controls. Fig. 1 presents these data in graphic form, the gain in grams of hemoglobin being plotted along the abscissa, and the percentage of cases along the ordinate. When the mean values in the separate groups are compared, the difference between the controls and the treated cases is not statistically significant (Table 1, Column E).

Comparison of the hemoglobin values of the treated groups and the controls at term failed to reveal any significant differences between the two (Table III). Further, while 51 per cent of the controls were anemic at term, 27 per cent of the treated group were still anemic at that time.

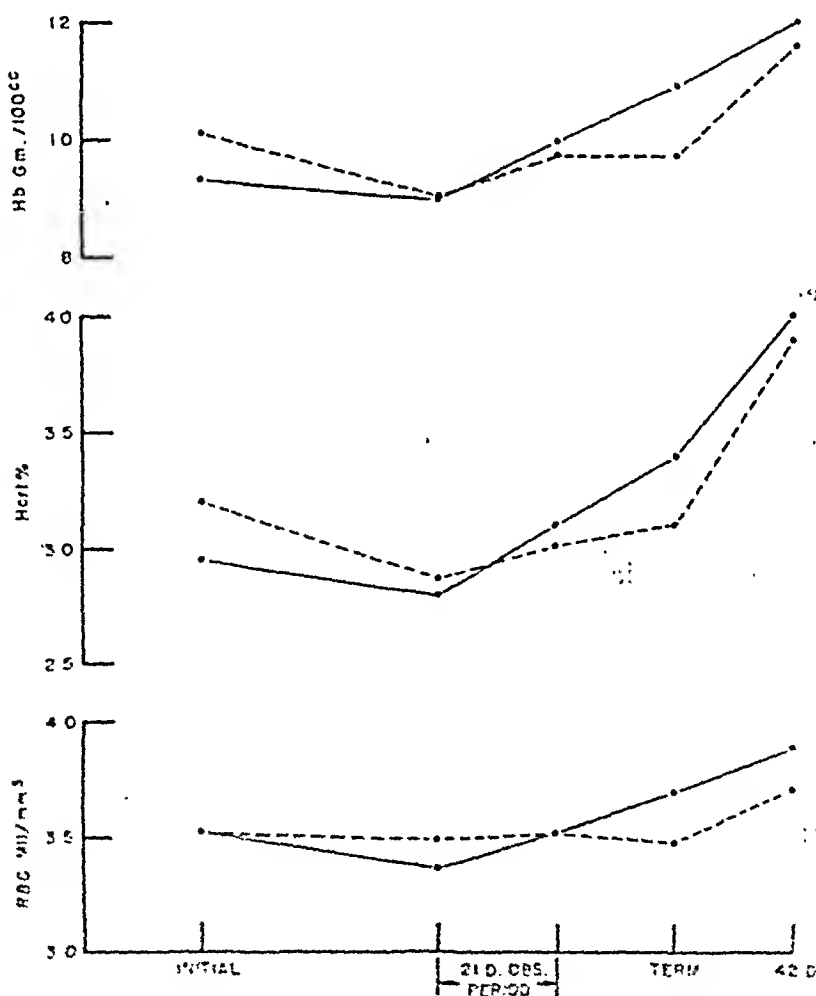


FIG. 2.

Many patients did not return for postpartum examinations, and therefore data were not uniformly available for comparison. The hematologic values of both groups, however, showed a rapid return to normal levels during this period (Fig. 2).

Diet histories of forty-two patients were analyzed by our nutritionist. Using the National Research committee's criteria for iron, and Burke's criteria for protein, she classified the diets as follows: poor iron and poor protein intake—14 per cent; poor iron, fair protein—31 per cent; poor iron and good protein—17 per cent. Thus 62 per cent had a low intake of iron. However, these diets may not be as deficient as they seem to be because they were based on patients' estimates, and we have learned that they are inaccurate and that the food must be weighed and recorded immediately. We are now doing this.

In certain cases transfusions of whole blood served as the principal therapeutic agent as indicated above. In these, transfusions were given as emergency measures because of rapidly falling hemoglobin values. Also, in five of the controls and in eleven of the treated cases, transfusions were administered after the completion of the twenty-one-day observation period when the patient had reached term before the hemoglobin had returned to normal levels. No hematologic data on the transfused cases are included here, as blood was uniformly given in quantities adequate to bring the hemoglobin to normal levels.

Discussion

The plasma volume during pregnancy increases 25 per cent and the red cell volume only 23 per cent, thus accounting for the physiologic anemia of pregnancy.¹² Reported bone marrow studies have revealed a normal erythroid pattern, and served to confirm the concept that this condition arises from hydration alone.

The cases in the present study represent those in which the hematologic findings fell below the minimal physiologic values. Changes in the peripheral blood may reflect both pathologic and physiologic processes simultaneously and their detection is characterized by certain inherent errors.² As a result of these factors the effects of any therapeutic agent must be evaluated cautiously.

Classically, microcytic hypochromic anemias are associated with iron deficiency. During pregnancy an inadequate diet, defective absorption from the gastrointestinal tract, and increasing fetal demands have been accused of precipitating this condition. Wolff and Limarzi^{13, 14} report a normoblastic hyperplasia of the bone marrow in such cases. These workers and others^{1, 5, 6} conclude that these anemias are the result of an iron deficiency and can be corrected by administering simple iron salts. Some workers stress the importance of diet in their prevention and correction.^{1, 15, 17} Others indicate that although an adequate diet is important from the standpoint of maternal health, the quality of the diet has little effect on the hematologic findings except in the extremes.^{3, 8, 16} Changes in the gastrointestinal secretory function occur in most pregnant women,¹⁷ yet no significant correlation exists between the decreased gastric acidity and the incidence of anemia.³ Further, studies with radioactive materials during pregnancy have revealed that iron is absorbed at two to ten times the normal rate.¹⁸ The amount of iron necessary for fetal growth is negligible during the first twenty-eight weeks and yet it is during this period that there is the greatest fall in the maternal hemoglobin concentration. It is only during the last twelve weeks, when the fetal weight increases from approximately 1,000 Gm. at twenty-eight weeks to 3,400 Gm. at term, that the iron requirement of the fetus becomes appreciable. But even at term, when the actual amount of iron required by the fetus is greater, the total fetal content is only 280 mg., which could be furnished by the iron from 600 c.c. of maternal

blood. Furthermore, it is during this last twelve weeks that the maternal hemoglobin concentration is either stationary or is increased. Thus, during the maximum fetal requirement, the hemoglobin concentration also increases.^{2, 8}

The results of the present study indicate that during pregnancy the rate of hemoglobin formation is not significantly altered by the administration of iron alone or in combination with accessory substances. In the light of the foregoing material this suggests that these anemias are not due to a simple iron deficiency, but that some other factor is lacking or that the defect lies in the mechanism of postabsorptive iron utilization.

The "pernicious-like" or megaloblastic anemia of pregnancy occurs only rarely.¹⁹ Several workers suggest that the diagnosis can only be made from studies of the bone marrow and that the peripheral blood findings are often misleading.^{13, 14, 20} It is unlikely that the macrocytic anemias in the present series are examples of the megaloblastic type of anemia.

Summary

Two hundred fifty cases of anemia in pregnancy were studied to evaluate the effects of treatment with iron alone and in combination with accessory factors. Controlled observations indicate that the administration of these substances does not increase the rate of hemoglobin formation significantly.

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ANTENATAL BLOOD GROUP DETERMINATION*

A Preliminary Report

S. H. POLAYES, M.D., SAMUEL LUBIN, M.D., AND JAMES McNALLY JR.
BROOKLYN, N. Y.

(From the Department of Pathology, Prospect Heights Hospital, and the Department of Pathology and Obstetrics and Gynecology, Cumberland Hospital)

IN THE course of a previous study¹ on isoimmunization with the A and B agglutinogens, it became apparent that a high anti-A or anti-B agglutinin titer in the serum of a pregnant woman is an indication of isoimmunization of the mother against the corresponding antigen in the fetus. In the case of a primipara, the immunization was naturally ascribed to the fetus of the existing gestation, while in the case of a multipara, either the existing gestation or any of the previous pregnancies could have acted as the immunizing agent.

In order to obtain more data on this hypothesis, a series of 100 pregnant women with blood groups O, A or B were chosen for study. Among them were 19 cases of heterospecific pregnancy. In each of the 100 cases, the anti-A and anti-B agglutinin titer of the serum was determined. As a control series, the bloods of 50 nulligravidas (O-A-B) who were never subjected to immunization by pregnancy or injection of blood were similarly titrated. In the pregnant women with children of blood groups compatible with their own, the average anti-A or anti-B titer of their serum did not exceed 1:500, and in no instance was the titer found to be above 1:1,280. In the series of nulliparas, about 95 per cent of the cases showed a titer ranging from 1:10 to 1:300. In no instance did the titer exceed 1:1,280. In neither of the latter two groups was there a single instance in which the anti-A or anti-B agglutinin titer reached a level of 1:2,000. In contrast to these values, the women with heterospecific pregnancy showed a much higher titer. In the majority of these instances it ranged from 1:500 to 1:5,000, and some reached values as high as 1:20,000 or more.² Titers of 1:2,000 or over were considered significant, since, as stated above, none of the nulliparas nor multiparas with babies of compatible blood groups showed such high values. Therefore, this titer was arbitrarily chosen as a base line above which any agglutinin titer would indicate isoimmunization against its specific antigen A or B. Thus, a woman of group B, whose serum showed an anti-A agglutinin titer of 1:2,500, was presumed either to be bearing (particularly of a primigravida), or to have previously borne a group A offspring. This presumption was confirmed in each case in which the agglutinin titer exceeded 1:2,000, as seen from Table I.

Comments

A study of Table I suggests that it may be possible to foretell the baby's blood group from a study of the titer of the group specific agglutinins in the serum of the mother. In several instances (not included in this table) in which the mother's serum showed an agglutinin titer approximating 1:2,000, but in which the mother was delivered of a group O baby, examination of her pre-

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TABLE I. ANTENATAL BLOOD GROUP DETERMINATION BY ANTIBODY TITRATION OF MOTHER'S SERUM (ANTI-A AND ANTI-B AGGLUTININ TITERS EXCEEDING 1:2,000)

CASE NO.	NUMBER OF PREGNANCIES	MOTHER'S GROUP	TITER	CHILD'S GROUP
35	1	O	Anti-B 2560	B
38	9	O	Anti-B 20,480	B
39	1	O	Anti-A 5120	A
42	1	O	Anti-A 2560	A
43	2	B	Anti-A 2560	AB
44	1	O	Anti-A 5120	A
76	1	A	Anti-B 2560	AB
86	1	O	(Anti-A 5120) (Anti-A Milk 5120)	A
88	1	O	Anti-A 20,000	A
103	2	O	Anti-A 5240	A
110	3	O	Anti-A 5120	A

vions offsprings showed them to belong to group A, B, or AB, as the case may have been. While a titer lower than 1:2,000 in a group O mother did not exclude the possibility of a group A or B offspring, the reverse was not true. No instance was found in which a mother with an agglutinin titer of 1:2,000 or over did not have an offspring with the corresponding specific antigen. Admittedly, the present series is not a very large one, but the nonstatistical evidence thus far may be considered quite striking. A case in point is case 43. The mother here is a group B, and therefore normally should have anti-A agglutinin in her serum. But the fact that the titer of the agglutinin was found to be as high as 1:2,500 led to the presumption that the offspring in utero must possess the A antigen, since, as far as could be determined, the mother had not been exposed to immunization with the A antigen previously. As is seen from Table I, this was a correct presumption, since blood grouping tests after birth proved the child to be a group AB. That this reasoning is equally applicable to instances of anti-B agglutinin, is borne out in case 76, where the anti-B agglutinin in a group A mother was found to be 1:2,560. The prediction that the yet unborn offspring contained the B antigen was confirmed, the child having been found to be a group AB at birth. Incidentally this baby was a girl, one of a twin, the other being a boy and a group A.

The highest titer in the tabulated cases was 1:20,000 or slightly above. This value was found in one case of a primipara and in another of a multipara (a para ix), showing that the titer of the antibody does not depend upon the number of pregnancies.

Case 86 showed an anti-A agglutinin titer of 1:5,120 in the milk as well as in the serum; hence (as in the case of Rh isoimmunization) the contraindication for breast feeding these infants.

The preponderance of group O mothers in the above table is probably a hapchance in this particular group of selected heterospecific pregnancies. Group AB, of necessity, had to be excluded from this series, since there are no anti-A or anti-B agglutinins in their serum.

The titers given are those obtained by the agglutination (saline dilution) technique. With the so-called conglutination technique (using homologous or AB serum as a diluent) much higher values were obtained in most, although not all of the cases. In fact, in a number of instances the "conglutinin" titer was considerably lower than the agglutinin titer.

Conclusions

1. In heterospecific pregnancies the anti-A and anti-B agglutinin titer in the mother's serum may rise to much higher levels than those found in nulliparas, or in mothers with offsprings of compatible blood groups.

2. When the anti-A or anti-B agglutinin titer in a primigravida's serum rises to a level of 1:2,000 or over, it may be presumed that the fetus in utero possesses in its blood the corresponding antigen A or B. In the case of a multipara, the immunizing A or B antigen will be found to be present in at least one of her previous children or in the offspring of the present pregnancy.

3. In primiparas and in certain multiparas with heterospecific pregnancy, the baby's blood group sometimes may be determined antenatally by the titration of the group specific antibodies in the mother's serum.

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MESODERMAL MIXED TUMOR OF THE VAGINA: REPORT OF CASE

GEORGE H. MURPHY, M.D., AND JAMES W. DESHANE, M.D., ROCHESTER, MINN.

(From the Department of Pathology, Mayo Foundation, and the Section on Pediatrics, Mayo Clinic)

THE following case, while primarily a pathologic problem, presents features of interest to the clinician as well. This report is of the third mesodermal mixed tumor diagnosed at the Mayo Clinic, two cases of such a tumor of the uterus having been reported by McDonald, Broders and Counseller; the tumor in the case reported herein is the first such tumor of the vagina found here.

Report of Case

A white child, 33 months of age, was admitted to the clinic on Nov. 6, 1946. Obstetric and family histories were irrelevant. About November, 1945, the parents had noticed the child scratching the vulva and saw a little blood. Examination by their local physician in February, 1946, had revealed a small tumor presenting at the vulva. The tumor was excised in March, 1946; the histologic diagnosis was "botryoid sarcoma (rhabdomyoma) of the vagina." The operative site received radium therapy seven months prior to her admission to the clinic, and the radium therapy was followed by roentgen therapy over a period of about two months. The child was apparently well for another two months but then more vaginal bleeding was noted and she was given further roentgen therapy. On admission to the clinic she presented no actual signs of distress, but the parents said she held back urine as long as possible. A satisfactory examination was not possible as the child was too apprehensive, but a soft mass was palpated in the vagina.

At operation on Nov. 8, 1946, a soft, polypoid tumor mass was found completely filling the vagina. The mass was removed, for the most part, and was found to originate on the right anterior wall of the vagina over an area of 5 by 2 centimeters. Because of the malignant nature of the tumor, as confirmed at operation by examination of a fresh frozen section, and its infiltration of at least the vaginal wall, the surgeon did not feel that a sufficiently radical operation could be attempted. The patient was discharged a few days later in good condition, but the parents were told that the prognosis was extremely grave.

Pathologic Findings.--The tumor, in pieces, weighed 24 Gm., forming an aggregate mass about 2.5 by 6 by 4 centimeters. It had the appearance of a group of polyps each about 2 cm. in diameter, the classical so-called botryoid morphology. The surface was smooth and gray-white except for a few hemorrhagic areas. The tumor was of firm consistency and could be cut easily; the cut surface was homogeneous and glistening.

Representative portions of the tumor were fixed in 10 per cent solution of formalin (3.8 per cent solution of formaldehyde), absolute alcohol, and Zenker's solution. Paraffin sections were stained by hematoxylin and eosin, Masson trichrome, Bodian and elastin H methods; sections also were stained for mucin by a modified Mayer mucicarmine⁴ method and for glycogen by the Best carmine method.

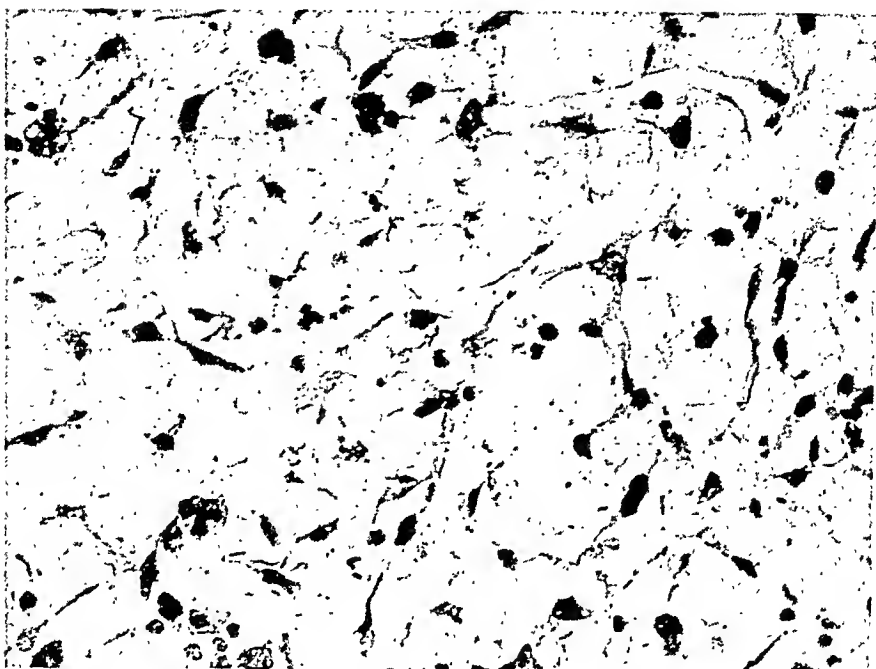


Fig. 1.—Myxomatous connective tissue network (Bodian $\times 335$).

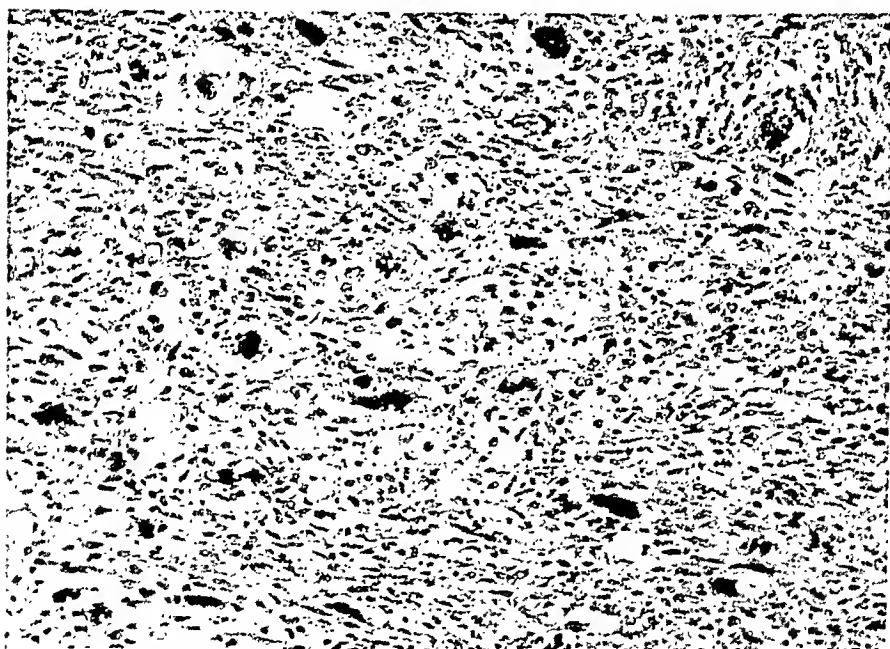


Fig. 2.—Plump spindle cell stroma with giant cells (hematoxylin and eosin $\times 100$).

Histologically the greater part of the tumor consisted of myxomatous connective tissue: spindle and star-shaped cells connected by delicate strands to form a network (Fig. 1). In other more cellular areas plump spindle cells with prominent nuclei and nucleoli and with mitotic figures were seen; interspersed were multinucleated tumor giant cells with large, often deeply staining nuclei and scanty cytoplasm (Fig. 2). Still other cellular areas showed rather irregular, round, or elongated cells, many with longitudinal striations and some with well-defined cross striations (Fig. 3): young striated muscle cells; scattered among these were embryonic myoblasts, large, often multinucleated cells

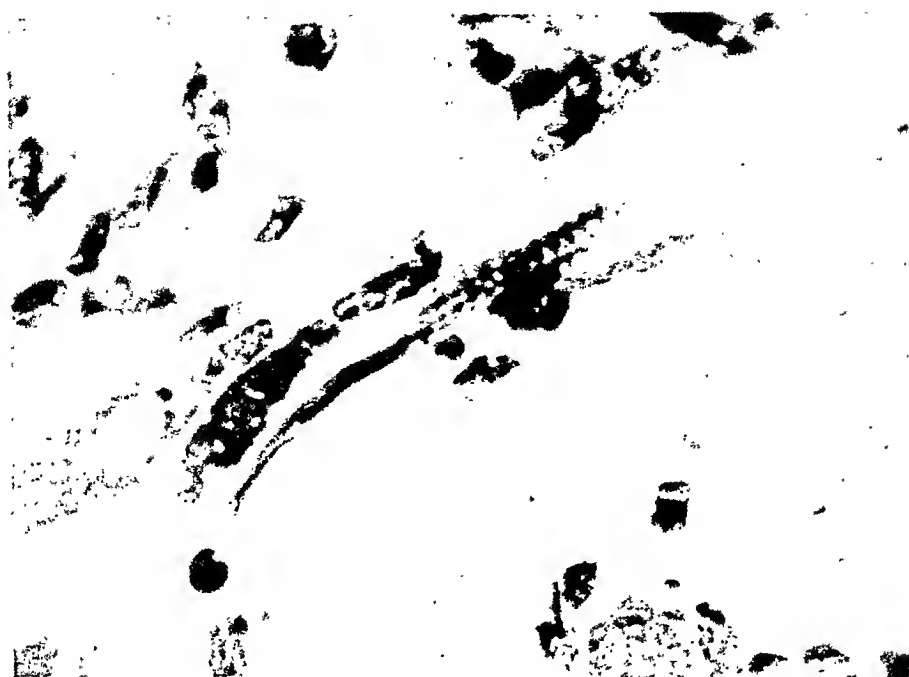


Fig. 3.—Young striated muscle fiber (Bodian $\times 1,000$).

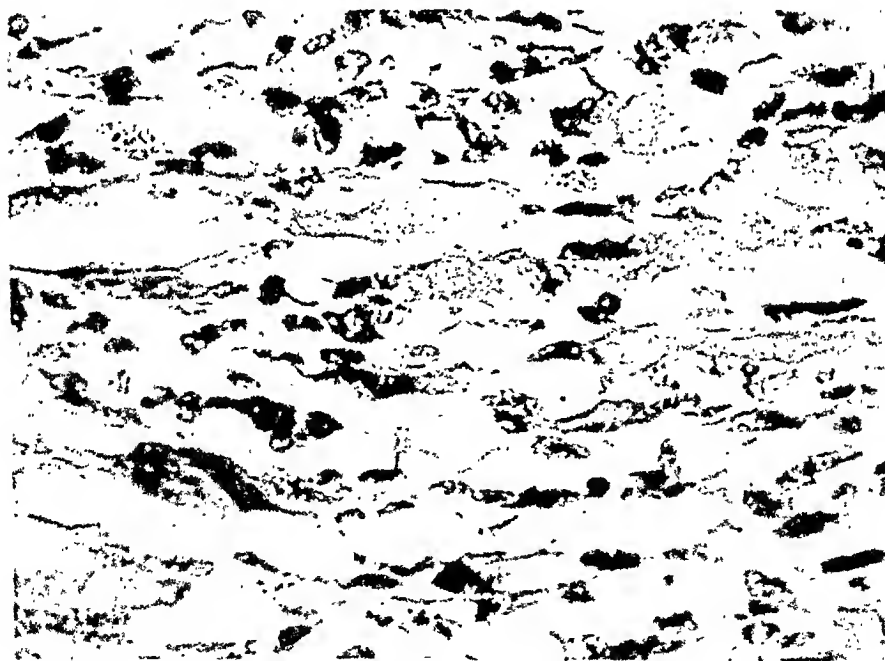


Fig. 4.—Myoblasts with myxomatous tissue matrix (Bodian $\times 470$).

with a relatively large amount of granular cytoplasm (Fig. 4). Some areas showed a considerable amount of collagen, but no cartilage or bone was found in the sections examined. Adult type squamous epithelium covered the surface of the tumor. Staining for mucin gave positive results in the myxomatous appearing areas and some extracellular and intracellular glycogen was noted. A few blocks showed gross degeneration with hemorrhage, and infiltration with acute and chronic inflammatory cells, doubtless a consequence of the radiation therapy.

Mesodermal mixed tumors form an ill-defined group of malignant neoplasms of the uterus, cervix, and vagina. By definition they are monodermic in origin, as opposed to the origin of teratomas which is tridermic, they develop from mesoderm and they consist of heterotopic and highly malignant tissues.

The literature contains confusing reports as to the nature and incidence of these tumors. McFarland,¹² in an extensive review of the subject, listed 116 different names from the literature for mesodermal type tumors of the genital tract; among the best known was the term "botryoid sarcoma" after the "traubiges Sarkom" of Pfannenstiel (1892). McFarland suggested the name "dysontogenetic tumors" for the whole group. The bulk of his data is not in the literature, but Amolsch would seem to have reviewed it when he reported 447 cases of mesodermal mixed tumors of the uterus, cervix and vagina, so diagnosed on the basis of the presence of embryonic myxomatous tissue. He and subsequent writers followed the terminology of Kehrer and called them all "mesodermal mixed tumors." Lebowich and Ehrlich⁹ and Ehrlich⁵ limited the group sharply by demanding the finding of embryonal striated myoblasts in accordance with the criteria set forth by L  wen; they could find reports of but fourteen such tumors of the body of the uterus in the literature. Glass and Goldsmith were not quite so exacting in their requirements and found records of ninety-four mesodermal mixed tumors of the uterine body and cervix. The incidence of the vaginal group is even more uncertain. Kehrer listed reports of nine vaginal sarcomas of children that showed heterotopic mesodermal tissues, usually embryonal striated muscle cells. McFarland,¹¹ in 1911, found reports of thirty-four "botryoid vaginal sarcomas," and by 1935¹² he had raised this figure to seventy-four. Bergstr  m, in 1936, added twenty to McFarland's original thirty-four cases. Undoubted new cases have been reported infrequently in the last twenty-years; we could find but seven in the literature,^{1, 2, 12, 18, 19} and none since 1939. It is apparent that the wide variation in all these figures is due to differing criteria of diagnosis; this variation does not, however, detract from the interest in, or the importance of, the group.

The consensus as to etiology favors a theory of cell rests²⁰ that is, the persistence in the genital tract, of pluripotent embryonal mesenchymal cells, capable of producing varied mesenchymal tissues. Some investigators,^{15, 17} however, favor a theory of metaplasia. Thus McDonald, Broders, and Counseller suggested that these tumors arise by a process of dedifferentiation of the endometrial stroma cells, after which differentiation takes place into various types of mesodermal structures. In both of their mesodermal mixed tumors of the body of the uterus they could trace the development of fibroblasts of the endometrial stroma into cartilage, and they considered these tumors to be true endometrial sarcomas.

Mesodermal mixed tumors are found in the uterine body, cervix, and vagina. Those of the uterine body are commonest in the menopausal or postmenopausal age groups, those of the cervix are commonest in the reproductive period, while those of the vagina have all occurred in very young patients, mostly those less than three years of age.

Because of the varying criteria of diagnosis, it is difficult to assess the relative incidence in the various sites. Glass and Goldsmith gave the ratio of those in the body of the uterus to those in the cervix as 1.6:1, while Lebowich and Ehrlich, with their stricter criteria, gave a ratio of 1:3. Shaw found those of the body of the uterus slightly less common than those of the cervix, a ratio of about 1:1.5. As has been indicated, the number of vaginal tumors is uncertain, but they would seem to be the most common of the three.

Clinically, there is little that is extraordinary about mesodermal mixed tumors. The signs and symptoms closely resemble the rather vague ones associated with adenocarcinoma of the genital tract of women, vaginal bleeding and discharge being the commonest signs. Such tumors of the vagina may first be noticed when they present at the vulva.

Grossly, mesodermal mixed tumors of the uterus appear often as single or multiple polyps, while the cervical and vaginal tumors may resemble a bunch of fused polyps, the grape-cluster effect that led earlier observers to name them "botryoid sarcomas." It should be noted that a single polypoid mesodermal mixed tumor may be indistinguishable grossly from a benign polyp of the genital tract.

The microscopic picture varies greatly with the individual tumor, and there is no constant difference between those of the uterus, cervix and vagina, except that neither bone nor cartilage has been found in those of the vagina.^{16, 18} They are true mixed tumors and contain numerous elements of mesodermal origin. All observers have agreed on the presence of myxomatous tissue, though not all have agreed on its nature; probably, however, it is embryonal mesenchymal tissue.²⁰ In addition there may be cartilage, striated and smooth muscle, myoblasts, bone, and so forth. Glandular structures, even adenocarcinoma, have been reported as occurring in the uterine tumors,^{5, 8, 9, 12, 13} but these were probably incidental inclusions of benign or malignant endometrial glands.^{13, 15} The histologic diagnosis of mesodermal mixed tumor may be difficult and many sections may be necessary to demonstrate heterotopic mesodermal tissue. As has been indicated, definite diagnostic criteria have not been universally accepted, but we agree with Morehead and Bowman¹⁴ in the belief that it is unwise to exclude all but those containing striated myoblasts since mesodermal mixed tumors are a pathologic entity and a group clinically.

The prognosis in all three types is uniformly bad, regardless of therapy. The over-all mortality rate has been given as 95 per cent¹; only one five-year and one ten-year cure have been recorded.⁶ The tumors have a marked tendency to local recurrence and extension after even the most radical operation, and death from local extension or from general metastasis may be expected to occur in six to twelve months.^{1, 6, 9} Metastasis to distant sites is, however, a relatively infrequent occurrence.^{3, 16}

Comment

The case reported herein would seem to be a typical example of a mesodermal mixed tumor of the vagina. Besides a myxosarcomatous stroma, the tumor contained myoblasts and striated muscle fibers, thus qualifying for the diagnosis in its most limited sense.^{5, 9} The occurrence of a positive result in staining for mucin which refutes Pfannenstiel's contention that the so-called myxomatous tissue is actually mere edema, has been reported also by previous observers.^{9, 15} The presence of glycogen is further evidence of the embryonic nature of the tumor tissue.

This case has been presented because of the rarity of the condition and to bring the entity to the attention of clinicians and pathologists alike. On gross, and even on microscopic examination, such a tumor, seen at an early stage, might easily be dismissed as a degenerating simple polyp, only to have the patient return with an infiltrating neoplasm obviously of high-grade malignancy. This has been a frequent occurrence in the recorded cases and may explain, in part, the extremely high mortality rate.

In the present case the diagnosis was made early, but in spite of local excision and radiation therapy the tumor advanced rapidly. In the light of reports in the literature and in view of the very malignant nature of these tumors, it would seem extremely doubtful that even radical operation, performed when the diagnosis was first made, would have altered, in any way, the course of the disease.

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LATE RECURRENCE OF CERVICAL CARCINOMA FOLLOWING RADIATION THERAPY

HAROLD SPEERT, M.D., NEW YORK, N. Y.

(From the Gynecological Service of the Roosevelt Hospital)

MORE than one-half of the patients with carcinoma of the cervix who have been unsuccessfully treated by irradiation at the Roosevelt Hospital showed a recurrence of their tumor within a year following treatment. Tumor recurrence after five years is distinctly unusual. This fact has served as the justification for the reporting of cervical cancer statistics in terms of five-year cures. Most gynecologists consider patients completely cured who survive this period with no clinical evidence of the disease.

Cervical cancer does not always run so rapid a course, however. New concepts of the pathology and biology of the early stages of the disease have been developed during recent years. Lesions which formerly were considered benign or of questionable malignancy have been associated with genuine cancer sufficiently often, either by the observation of the untreated patient during the ensuing years after biopsy, or by more intensive examination of the original specimen to merit the diagnosis of cancer themselves.

Smith and Pemberton (1934) reported one case in which six years elapsed between the original biopsy, which later was diagnosed pathologically as carcinoma, and the development of the lesion to the readily recognizable clinical entity; and in another they reported an incubation period of possibly twelve years. In a case reported by Stevenson and Scipiadès (1938) clinical cancer of the cervix did not appear until eight and one-half years after the microscopic diagnosis of noninvasive carcinoma. More recently Taylor and Guyer (1946) have described another case in which seven years elapsed between a positive biopsy and the ultimate diagnosis of clinical carcinoma. It has been shown by Te Linde and Galvin (1944) that lesions diagnosed as intraepithelial carcinoma, noninvasive carcinoma, or carcinoma in situ, previously believed by some pathologists to be only precancerous, usually are found to contain regions of invasiveness if the specimen is sectioned serially. These observations strongly indicate that cancer of the cervix may develop quite slowly in its very early stages.

The purpose of this communication is to record two extraordinary cases which show that cervical carcinoma may progress slowly, or perhaps even lie dormant for long periods after treatment by irradiation, during its later clinical stages.

CASE 1.—A. G. (R. H. No. 394167) was a 52-year-old white nulliparous divorcee with a history of four spontaneous abortions. She was treated for primary carcinoma of the cervix in April, 1922, at the age of 35 years, at the Memorial Hospital. Her cervix at that time, according to a report from

Memorial Hospital, was about 5 cm. in diameter with a hard, nodular surface that was beginning to ulcerate in places. The uterus was moderately movable, but there seemed to be some "shortening of the right parametrium." Biopsy report by the late Dr. James Ewing stated "epithelioma, type uncertain" (Fig. 1). Treatment consisted of 100 mc. hours of radon administered in each of three positions by vaginal bomb on April 17, 1922, and 3,000 mc. hours administered by platinum cervix tandem on the following day. This was followed by a cycle of low voltage pelvic x-ray to two anterior and two posterior fields on April 19 and 20. The patient remained under the observation of the gynecologic department of the Memorial Hospital for twelve and one-half years, until Nov. 21, 1934. There was no evidence of residual or recurrent tumor during this period.

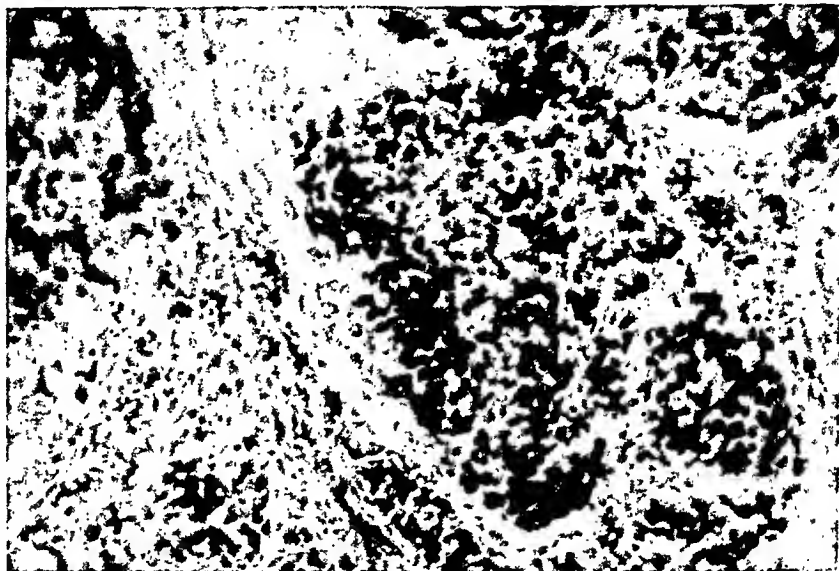


Fig. 1.—Case 1. Cervical biopsy specimen, showing anaplastic epidermoid carcinoma.

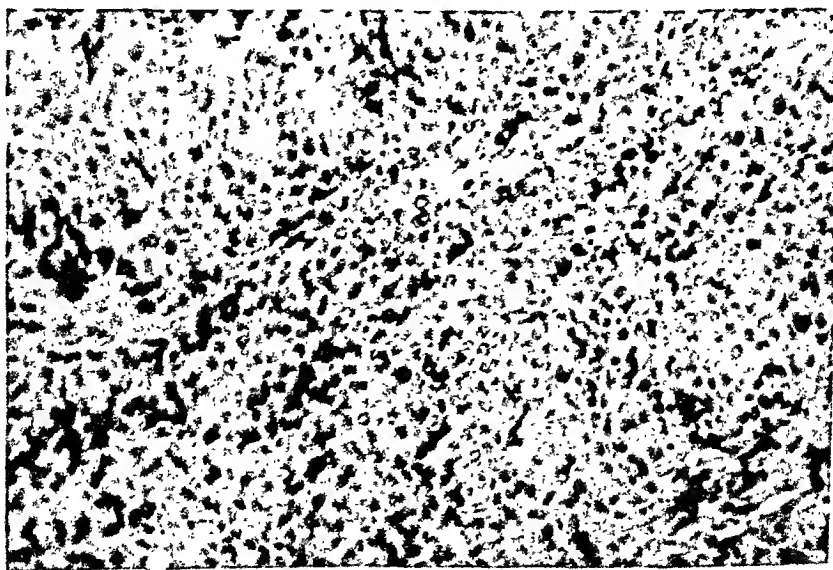


Fig. 2.—Case 1. Cervical tumor removed at autopsy seventeen and one-half years later, showing same cell type as original biopsy.

She was admitted to the Roosevelt Hospital Sept. 21, 1939, complaining of vomiting, diarrhea, and lower abdominal pain of eighteen days' duration. A hard, irregular, movable mass, about 15 cm. in diameter, occupied the right lower quadrant of the abdomen. The vagina was constricted and filled with hard friable tumor. Biopsy of this tumor showed only granulation tissue. The patient's serologic tests for syphilis were positive. Her blood urea nitrogen was 85 mg. per 100 c.c. the day after admission and rose in three days to 115. Intravenous pyelograms showed no excretion of the dye from either kidney. The patient developed a toxic erythema and died Oct. 18, 1939.

At autopsy the anatomic diagnosis was "carcinoma, primary in cervix, with extension to fundus, bladder, rectum, ovaries, Fallopian tubes, and metastatic invasion of periaortic lymph nodes, liver, and diaphragm; ureteral obstruction, bilateral, with hydroureter and hydronephrosis." The pelvic organs were greatly distorted by infiltration of the tumor. The outline of the cervix was destroyed by ulceration and necrosis, the process extending into the vaginal walls. More than three-fourth of the uterus was involved in the tumor mass. The endometrium was thin and smooth except for a single small polyp. Microscopically the tumor showed irregular masses of undifferentiated oval cells supported by small amounts of stroma, with almost complete lack of organization. The nuclei were hyperchromatic and mitoses were fairly numerous (Fig. 2). Dr. Walter Brandes, Pathologist to the Roosevelt Hospital, and Dr. Ewing compared sections of this tumor with that of the original cervical biopsy of seventeen and one-half years previously and agreed that they could not distinguish the one from the other, so completely similar were they in histologic detail.

CASE 2.—N. M. (R. H. No. 13502 and No. 28803), a 33-year-old married Jamaican Negro woman with two children, was admitted to the Roosevelt Hospital for the first time on April 1, 1925, complaining of dysmenorrhea and intermittent backache and vaginal discharge for two years. Her menses were regular, her last period having begun March 24. Her cervix was large, bilaterally lacerated, eroded, and a thick purulent discharge was in the canal. The fundus was of normal size, retroverted, and a small fibroid was present near the right cornu. On April 6, 1925, curettage, tracheloplasty (Schroeder), left salpingo-oophorectomy, hysteropexy (Simpson), and appendectomy were performed. Chronic salpingitis was encountered. Histologic examination of the two pieces of cervical tissue removed at operation revealed epidermoid carcinoma. The original specimen, unfortunately, could not be found for re-examination, but the pathologic report, which is quoted herewith, leaves little doubt as to the accuracy of the diagnosis: "Sections of the cervix through the region of the external os show well-preserved stratified squamous epithelium and a few typical cervical glands. In addition round masses of neoplastic epithelial cells are present some distance beneath the surface epithelium. Individual cells show pale staining cytoplasm; the nuclei vary in size and shape and are hyperchromatic. Mitoses are present. Occasionally a small cord of these cells lies free in connective tissue spaces. Lymphocytes surround the tumor. Some of the epithelium is keratinized. The tumor masses invade the cervical glands in some places." On April 16, 1925, 50 mg. of radium was applied in the cervical canal for twenty-four hours; and between April 20 and July 14 the patient received a filtered x-ray treatment through each of six pelvic portals, with the 200 kv. machine at a skin-target distance of 50 cm.—three exposures for thirty minutes each, and three for forty minutes.

Following her discharge from the hospital the patient returned at regular intervals to the Out-Patient Department until 1931. She was not seen again until Nov. 9, 1944, at the age of 53 years. She now stated that during the past

few years, since 1936, she had experienced a foul, blood-tinged vaginal discharge, although she had not menstruated since her previous radiotherapy. Pelvic examination disclosed a hard, friable tumor mass which involved the cervix and adjacent vaginal walls with slight fixation of the parametria. Biopsy of the cervical tumor showed epidermoid carcinoma, grade III. The surface epithelium was ulcerated by a neoplastic growth composed of squamous epithelium with limited keratinization. The cells were loosely arranged, had large nuclei, and numerous mitoses (Fig. 3). The patient's serologic tests for syphilis were positive. During the next few weeks she received twenty deep x-ray treatments through four pelvic portals, a total dose of 6000 r. Several episodes of vaginal bleeding occurred in the course of this treatment, each being managed with vaginal packing and blood transfusion. She received antisiphilitic therapy with bismuth at the same time. The patient was readmitted on Feb. 12, 1945, because of abdominal cramps, weight loss, uremia, and anemia. The tumor had extended to the bladder and rectum with the formation of a vesicovaginal fistula and a rectovaginal fistula. Cystoscopic examination indicated blockage of the right ureter by the tumor. The patient died on May 16, 1945.

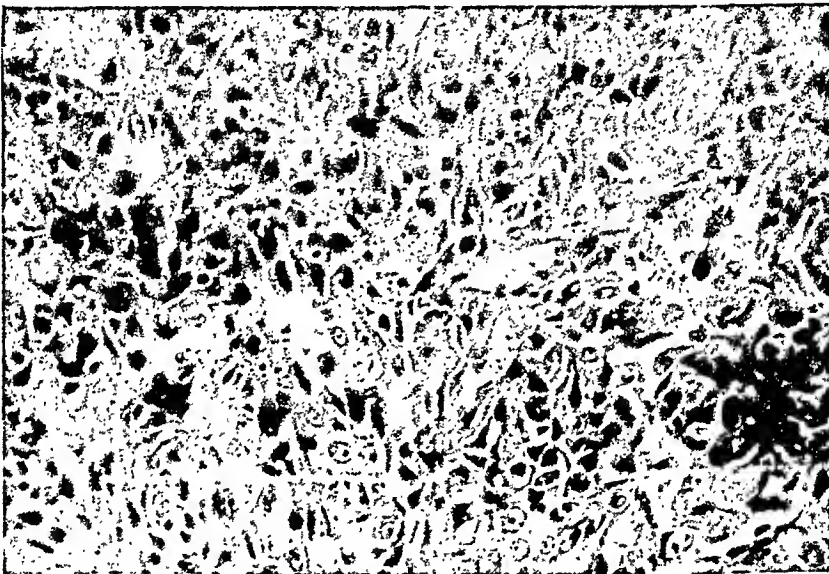


Fig. 3.—Case 2. Cervical biopsy specimen, showing epidermoid carcinoma, nineteen and one-half years after treatment.

Comment

It is impossible to prove that the secondary cervical tumors in these two cases represent recurrences rather than independent cancers. The fact that the histologic types of the secondary tumors correspond with those of the original biopsy specimens makes the presumption reasonable, however, that we are dealing with long delayed recurrences of previously treated cervical cancers. This presumption is strengthened in Case 1, because of the anaplastic nature of the tumor. Since this is the least common of the epidermoid cervical cancer types the chances of an independent new growth of the same type are small. Covington (1947), in reporting recently a similar case of recurrent carcinoma of the cervix seventeen and one-half years after radiation therapy, said that he had never seen a new cancer develop in a cervix which had been treated previ-

ously by radium. These two cases, therefore, are submitted as recurrent cervical cancers which appeared seventeen and one-half years and nineteen and one-half years after initial treatment, respectively. Covington's case and the present two represent the latest local recurrences of epidermoid carcinoma of the cervix of which I have been able to find record.

From a practical clinical standpoint it would seem safe to consider as probably cured any patient with cervical cancer who survives the standard five-year period without evidence of recurrence. Records of the Roosevelt Hospital contain 105 cases, exclusive of the 2 above, in which the time of recurrence could be determined in patients treated with radium. The time intervals are shown in Table I. The average time of recurrence was 14.5 months. Fifty-seven per cent of the recurrences were detected within a year of treatment, and only one recurrence was observed after five years.

TABLE I. INTERVAL BETWEEN TREATMENT AND RECURRENCE IN 105 CASES OF RECURRENT CERVICAL CARCINOMA

INTERVAL (MONTHS)	NUMBER	PER CENT
0-6	37	35
7-12	23	22
13-24	28	27
25-36	8	8
37-48	7	7
49-60	1	1
over 60	1	1

Summary

The average interval between treatment and recurrence in 105 patients with recurrent epidermoid carcinoma of the cervix treated with radium was 14.5 months. Fifty-seven per cent of the patients manifested their tumor recurrence within a year. Only one recurrence was observed after five years. Two additional cases are reported in which local recurrence of previously irradiated cervical cancer occurred seventeen and one-half years and nineteen and one-half years later, respectively.

Addendum: The present data are at variance with a recent report by D. G. Morton (Am. J. Roentgen, 57: 685, 1947). Of 45 patients with cervical cancer who survived five years after irradiation therapy, 13 (29 per cent) subsequently died of cancer.

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Special Article

PELVIC CANCER DELAY*

The Organization and Observations of the Philadelphia Committee for the Study of Pelvic Cancer

JOHN Y. HOWSON, M.D., PHILADELPHIA, PA.

THE high death rate from cancer today emphasizes the ignorance of its cause, the limitations of present forms of therapy, and the failure to diagnose it while still favorable for treatment. What measure of success we enjoy is limited to that small group of fortunate patients in whom an early diagnosis is achieved. A greater effort must be made to prevent its development and to find it at its inception.

The problems of making an early diagnosis of cancer have long been recognized. For instance, the very location of a malignant growth often precludes our ability to find it. In contrast, accessible lesions afford no reasonable excuse for delay in their early discovery. Most malignancies occurring in the female pelvis fall into this latter category. Basically, therefore, the early discovery of cancer so located is dependent on the prompt action of the patient at the first sign of trouble; and likewise on the physician's immediate discharge of his duty at her first visit.

It has been shown frequently that the physician is an important factor contributing to delay in the early diagnosis of cancer. The very life and death of an individual may depend on the physician's degree of suspicion of cancer, his ability to recognize its early stages, and upon his ultimate recommendation. If, as it seems, the physician is a contributor to delay in the diagnosis of early cancer, then something beyond mere criticism is indicated. Remedial suggestions have been made many times, but no practical educational program for the general practitioner or physicians in general has ever been established.

Two years ago a group of physicians in Philadelphia proposed a plan whereby they hoped to stimulate physicians to recognize their responsibility in regards to the diagnostic delay period in patients suffering with pelvic cancer. In brief it was proposed:

1. To form a committee of gynecologists who would study all pelvic cancer cases in Philadelphia with special reference to the sequence of events occurring between the onset of the patient's first symptoms, a definite diagnosis and adequate treatment.

2. To utilize the facts obtained from this study to inform the medical profession of their importance in diminishing the delay in diagnosis of pelvic cancer.

*Read before the Philadelphia Obstetrical Society, Feb. 6, 1917.

The project was accepted and sponsored by the Philadelphia Obstetrical Society. Such a committee was appointed and received the approval of both the Philadelphia Department of Public Health and the Philadelphia County Medical Society. Headquarters were established in the County Medical Society Building and the American Cancer Society granted funds, sufficient to permit the employment of a full-time investigator to carry out the actual work.

The principal hospitals of Philadelphia soon gave their full cooperation to this undertaking. They granted permission for the Committee's investigator to enter their wards and out-patient clinics for direct questioning of each patient suffering with pelvic cancer. At the present time the Committee has access to such patients in 19 different institutions, which include all of the teaching hospitals. A questionnaire designed for its brevity, clarity, and chronological disclosure of facts about the delay period has been used to help correlate and record the desired information.

Method of Utilization of Material

The Committee meets monthly. Prior to each meeting the cases investigated during the preceding month are classified into two main groups: those cases revealing no delay and those cases with an apparent delay. The cases with an apparent delay are then subdivided into three categories: (1) delay due to the patient, (2) delay due to the physician, and (3) delay due to both the patient and the physician. The cases showing physician delay are further scrutinized for detailed discussion at the time of the next meeting.

In March, 1946, the custom was instituted of inviting any physician intimately connected with the cases exhibiting delay to meet with the Committee to participate in the discussion. This was necessary for two reasons: The information obtained by our questionnaire was entirely that voiced by the patient. Knowing the frequent inaccuracy of patients' statements the Committee felt that in no case should the responsibility for delay be ascribed to a physician without affording him the opportunity to present the facts as he knew them. The second reason for inviting the family physician, and the main one, was to begin a program of education among the physicians of this city. Specifically the group wished to create a higher index of suspicion for pelvic cancer, emphasizing the importance of making adequate pelvic examinations and early diagnoses. The Committee was anxious to reveal the true causes of physician delay as they were brought to light by the survey and to take active steps to correct them.

Getting the busy doctor to attend the meetings at first posed a problem, since no physician is anxious to be censured or questioned as to his efficiency in the handling of his patients. In order to reach the physicians in question, a letter was written to each one, inviting him to attend the meetings to further disclose the details of the case history as he knew it. It was explained that the purpose of the Committee was not to ridicule or castigate anyone, but it was necessary to obtain all the facts before determining the existence of a true delay or what could be done to prevent a similar delay in the future. To date twenty-seven physicians have met with this Committee. The response and cooperation of these physicians have been most encouraging.

The meetings have been informal and friendly, yet the discussions have been serious and stimulating. The physicians who have met with the Committee have been dealt with in a friendly way and there has been a mutual exchange of ideas between the general practitioners and the specialists in Gynecology. When a

delay by the physician is disclosed, little emphasis and importance are placed on this in itself. The underlying reason for the delay is the important topic of discussion. For example, when the delay resulted from failure to take a biopsy, the discussion will evolve around the question of whether a general practitioner should attempt cervical biopsy. If so, what equipment should he have available? Should he biopsy all cervices showing erosion? How should he decide the need of a biopsy? At the conclusion of the discussion, the helpful suggestions and the constructive criticism have been a lesson to all present. The physician who failed to take the biopsy has been forgotten, and this is as it should be.

Summary of Results

Between Nov. 1, 1945, and Jan. 1, 1947, some 455 living patients with pelvic cancer were investigated. Of this number, in 145, or 31.8 per cent, there had been no delay. The remaining 310, or 68.1 per cent of the cases, demonstrated a lapse of one or more months from the time the symptoms were first noted until a correct diagnosis was made and adequate treatment instituted.

Number of cases investigated	455	
No delay	145	31.8%
Delay of more than one month	310	68.1%

Of these 310 cases showing a delay it was found that the patient alone was responsible in 197, or 63.6 per cent; the physician alone was at fault in 76, or 24.5 per cent, of the cases. In 37, or 12.0 per cent, of the cases, the patient and the physician were equally dilatory. Thus the combined total involving the physician was 113 cases, or 36.5 per cent.

Number of cases showing delay	310	
Responsibility—		
Patient	197	63.6%
Physician	76	24.5%
Physician and patient	37	12.0%

In 93, or 82.3 per cent, of the cases, one physician contributed to the delay. In 17, or 15.0 per cent, of the cases, two physicians were involved in the delay of each patient. Three physicians were dilatory in three of the cases, or 2.6 per cent. It should be noted that in the 113 cases showing physician delay there was a total of 136 doctors responsible—which truly is a more revealing index of the problem at hand.

Number of cases showing physician delay	113	
Delay by one physician	93	82.3%
Delay by two physicians	17	15.0%
Delay by three physicians	3	2.6%
136 physicians involved in 113 cases		

These figures demonstrate that the physician plays an active part in the problem of a delay in early diagnosis. Thus in a small way a program has been launched for educating the physician (be he specialist or general practitioner) to the opportunity afforded him to make an early diagnosis in cases of pelvic cancer. The Committee believes that such a program can become an influential contribution for obtaining earlier diagnoses in pelvic cancer and thus a better salvage of patients afflicted with this disease.

Editorial

ECLAMPSIA

Several reports on the etiology of eclampsia are based on the premise that the disease is primarily a hypertension due to spasm of the arterioles. Most investigators, however, believe that eclampsia—pre-eclampsia is a clinical entity in which there is first a water and salt retention due to an abnormal capillary permeability. Some of the patients develop hypertension (which may be compensatory), proteinuria, and a very few have various other symptoms and signs due to cerebral anemia, culminating in convulsions and coma.

Grollman stated that if the Goldblatt elamp is properly placed on the renal artery there is no increase in the blood pressure during pregnancy, or if there is a hypertension before pregnancy, that the blood pressure decreases to normal. The acute toxemia described by some investigators as a result of constricting the renal artery is due to too great a constriction. He thinks that the normal blood pressure is due to the increased vascular bed resulting from the pregnancy.

Smith and Smith still believe that a deficiency of estrogen and progesterone, as well as abnormal oxidation of the estrogens is associated with certain pathologic changes in the placental syncytium resulting in a failure of the latter to utilize chorionic gonadotropin. The result of this abnormal hormone and placental metabolism is the production of a protein similar to menstrual toxin. This toxin according to them is the cause of pre-eclampsia. They have treated a small group of patients with a protective pseudoglobulin which they think has resulted in clinical improvement. It is difficult for one to see any striking effects of this neutralizing protein fraction.

Grollman states that hyperfunction of the posterior lobe or the basophilic cells has no connection with the etiology of eclampsia or hypertension. He also states that it remains to be proved that hormonal aberration is the cause of toxemia and not the result of some fundamental process.

Several investigators have reported the production of the periportal hemorrhage and necrosis in experimental animals by various procedures. Dieckmann has observed several patients who showed no evidence of eclampsia prior to death, yet the liver showed the typical lesion of eclampsia. He believes that the periportal hemorrhages found in the liver are peculiar to the pregnant woman under certain conditions, but are not pathognomonic of eclampsia. A recent report indicates that thickening of the basement membrane is not always present in eclamptic patients. Thus there is no pathologic lesion either in the liver or the kidney characteristic of eclampsia.

Since the liver and kidney lesions are not peculiar to eclampsia—pre-eclampsia, and, since the Goldblatt kidney does not produce eclampsia, it seems that animal experimentation is of little value in determining the etiology of eclampsia.

Several reports indicate that there is no abnormal renal physiology in eclampsia—pre-eclampsia. This is difficult to believe, especially since all the studies were made when the patients were secreting urine and not during the anuric phase of the disease.

One investigator states that repeated injections of Veratrone (veratrum virides) does cause a reduction in blood pressure, but at the same time there is a marked reduction in urinary output. He concludes that the use of Veratrone is contraindicated in the treatment of pre-eclampsia—eclampsia.

Several reports have been published claiming that the injection of plasma has been of great benefit in the treatment of eclampsia. Eclampsia is such a protean disease, being readily curable if early delivery occurs, that it requires a large number of cases to properly evaluate a specific treatment.

Reports are still being published in which eclampsia is attributed to faulty diet. This seems difficult to prove and certainly in most clinics eclampsia is rare, but pre-eclampsia still occurs even in patients who have been on a reasonably adequate diet.

High spinal anesthesia, especially with the catheter technique, seems of proved value in the treatment of the cardiac failure with pulmonary edema that is such a serious complication of eclampsia. If this work is confirmed, it is the most important contribution to the treatment of eclampsia—pre-eclampsia that has been developed in the past decade.

Since eclampsia—pre-eclampsia is an entity peculiar to the human race, studies as to the etiology and treatment must be made on pregnant patients and not on animals.

W. J. D.

Necrology

FRANK FARROW SIMPSON, long associated as gynecologist with the hospitals of Pittsburgh, Pennsylvania; died on Feb. 10, 1948, in Honolulu, T.H., where he resided since his retirement about twenty years ago. He was born in 1868, graduated with a baccalaureate degree from the University of South Carolina in 1889, and received his M.D. at the University of Pennsylvania in 1893. He was President of the American Gynecological Society in 1917, Vice-President of the American Association of Obstetricians and Gynecologists in 1905, Secretary General of the Seventh International Congress for Obstetricians and Gynecologists in 1912, section chairman of the American Medical Association, in 1912, Chief of the Medical Section, Council of National Defense, 1917-1918, and Lieutenant-Colonel Medical Corps, United States Army.

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Cantone, C.: Carcinoma of the Stump After Supravaginal Hysterectomy, *La Ginecologia* 12: 285, 1946.

During the period between 1938 and 1944, carcinoma of the stump after supravaginal hysterectomy was observed in the Department of Obstetrics and Gynecology of Vercelli in 0.67 per cent of the cases.

Mortality rate, after total hysterectomies (excluding operations performed for carcinoma), reached 2.50 per cent, while in cases of supravaginals the mortality was reduced to 1.38 per cent. The number of total hysterectomies during the above-mentioned years was 182, the number of subtotal hysterectomies 595.

Cantone recalls the opinion of some gynecologists in this country, that in hospitals where hysterectomies are not very frequently performed, the supravaginal operation should be considered the method of choice, if a definite indication for a total hysterectomy is not present, but believes that the matter requires further investigation. GEMMA BARZILAI.

Furth, J., and Sobel, H.: Hypervolemia Secondary to Grafted Granulosa-Cell Tumor, *J. Nat. Cancer Inst.* 7: 103, 1946.

Hypervolemia (increased blood volume) occurs in mice engrafted with certain, but not all, strains of granulosa cell tumor. It amounts to over twice the average volume found in normal animals, or in mice bearing other tumors. There is an increase in plasma volume (in contrast with human polycythemia), a twofold increase in total red cells, and in cells per unit weight; and a slight fall in red-cell count and in hematocrit. At necropsy there is marked congestion of liver, spleen, adrenals, and bone-marrow. The hypervolemia does not parallel the tumor size, the amount of organ congestion, nor the extent of estrogenic change. It does not follow massive doses of estrogens alone.

These tumors evidently produce a substance which affects the blood volume mechanism, and cause the appearance of blood changes like those seen in pregnancy. The substance may be a hormone like those secreted by the adrenal cortex. IRVING L. FRANK.

Endocrinology

Baidins, Von A., Claesson, L., and Westman, A.: On the Influence of Roentgen Treatment Upon the Gonadotrophic Function of the Pituitary, *Gynaecologia* 122: 347-362, 1946.

The authors, reporting from the Woman's Clinic of Karolinska, Stockholm, attempted to re-evaluate the gonadotrophic function of the pituitary gland after x-ray treatment. In their opinions this problem was unsolved. The authors, therefore, investigated the influence of x-rays upon the gonadotrophic function of immature female white rats, using 61 animals of which 38 were in their study groups and 23 were employed as controls.

The essayists concluded that it was impossible to influence the pituitary gland of 27 white female infantile rats with small doses of x-ray, 2 to 45 roentgen units; and, in such cases, the ovaries could not be stimulated. The anatomic findings confirmed the biological studies. Dissection and histologic investigations did not show any special difference between the experimental and 12 control animals. Increased function of the pituitary could not be observed biologically or by morphologic changes.

The eight rats treated with 50 to 1,000 roentgen units, or their eight controls, did not reveal any irregularities of ovarian function nor histologic changes of ovaries or pituitary glands.

C. E. FOLSOME.

Gynecology

Matus, V., and Moreno, G. M.: Importance of Puncture of Cul-de-Sac of Douglas in Gynecology, *Bol. Soc. chilena de obst. y ginec.* 11: 23-27, 1946.

During the years 1944-45, pelvic puncture was employed 111 times. The indications were as follows: tubal pregnancy, 50; pelvic abscess, 35; postoperative complications, 8; peritonitis, 6; no diagnosis (blank puncture), 5; tuboovarian abscess, 4; infected hematocele, 1; ovarian cyst, 1; and ruptured bladder, 1.

The authors believe that pelvic puncture is a very helpful procedure. They compare its usefulness with three other procedures used in gynecology, namely, the Schilling hemogram, endometrial biopsy, and the Friedman pregnancy test.

J. P. GREENHILL.

de Moraes, A., and do Amaral, C.: Concerning Cases of Tuberculosis of the Female Genitalia, *An. brasil de ginec.* 22: 255-262, 1946.

During the last two years, the authors observed eight cases of tuberculosis of the female genitalia among 954 patients operated on at the Gynecological Clinic of the National Faculty of Medicine of the University of Brazil. This represents an incidence of 0.84 per cent. The authors discuss the diagnosis of this condition and they particularly emphasize the importance of making microscopic examinations of all tissue removed at operation.

Gynecologic Operations

Brindeau, A., Lantuejoul, P., and Hubert, L.: The Use of Ovular Membranes in Creation of an Artificial Vagina, *Gynec. et obst.* 45: 417, 1946.

A third successful creation of an artificial vagina, by a technique published by Brindeau in 1938, is recounted. With a sound in the bladder, and a guiding finger in the rectum, a channel is created through the perineum, between whatever labial structures are present. This channel is then lined with ovular membranes obtained at a simultaneous cesarean section. The membrane sac is anchored to the vault with a few sutures, and the free edges are united with the margins of the original U-shaped perineal skin incision. The lined canal thus produced is packed for a week with gauze soaked with horse serum, and for a second week with gauze soaked in cod liver oil. Thereafter the patient inserts a No. 20 Hegar bougie daily for six weeks to prevent stenosis during the healing process. The membranes are gradually replaced by epithelium, and the patient reported had a good functional result. The authors have done preliminary laparotomies in these cases.

IRVING L. FRANK.

Judd, George E.: Preservation of the Upper Pelvic Floor and Bladder Support in Total Hysterectomy, *West. J. Surg.* 55: 209, 1947.

A historical review of total hysterectomy is presented. The chief support of the uterus is the endopelvic fascia which covers the pelvic organs below the visceral peritoneum. In some cases the fascia is strengthened and forms true ligaments notably in the base of the broad ligaments; posteriorly it forms the uterosacral ligaments and anteriorly the uteropubic ligaments. Cystocele is primarily a hernia of the bladder through a break in the uteropubic fascia. Prolapse of the uterus results from laceration or stretching of the endopelvic fascia, laterally and posteriorly.

The author describes and illustrates his technique for total hysterectomy based on the above anatomic knowledge. The broad ligaments are cut and ligated, and the uterine vessels ligated and cut. A cuff of the endopelvic fascia is then made by a circular incision around the cervix. The anterior cuff is pushed down along with the bladder; the posterior is pushed along with the uterosacral ligaments, and the lateral or cardinal ligaments are dissected free of the uterus and ligated. The vagina is entered posteriorly, and a circular incision made to remove the uterus. Sulfanilamide powder is put in the vagina. The vaginal cuff is closed and then the fascial cuff, including the cardinal ligaments laterally and the uterosacral ligaments posteriorly, is sutured over the vaginal vault. Where a cystocele exists the uteropubic fascia is approximated to provide a new floor for the bladder. The entire area is peritonealized by suturing over with the peritoneal fold of the bladder.

WILLIAM BICKERS.

Menopause

Taylor, R. D., Corcoran, A. C., and Page, Irvine H.: Menopausal Hypertension: A Critical Study, *Am. J. M. Sc.* 213: 475-476, 1947.

The authors, reporting from the Lilley Laboratory for Clinical Research, Indianapolis City Hospital, followed 179 castrated women and twenty-one with the natural menopause. They demonstrated, in these cases, that arterial hypertension was no more common in them than in the general population. "Vasomotor instability," as exhibited by "hot flashes," perspiration, and tachycardia were not necessarily associated with hypertension, and their alleviation by estrogens need not affect arterial pressure.

The menopause seemed to intensify pre-existing psychonuroses. Despite severe neurotic behavior, hypertension did not develop within three or more years except in six of those 200 subjects. From these data the authors conclude that the relationship of the menopause and hypertension was incidental, and the loss of ovarian secretion was neither a primary nor a contributory cause of arterial hypertension.

C. E. FOLSOME.

Newborn

Rossi, Antonio: Weight and Length of Newborn, *Ginecologia* 12: 100, 1946.

Rossi reviews weight and length of newborn babies, and the weight of the placenta, of confinement cases in Novara, Italy, from 1937 to 1943. A definite decrease in weight, length of the babies, as well as a reduction in the weight of the placenta is noted. This applies to the population as a whole, as well as to different social and financial groups: housewives, factory workers, women from rural districts.

The average weight of the newborn babies for the entire population in 1937 amounted to 3,236 Gm., and in 1943 it decreased to 3,030.8 Gm. The average length of the newborn was 50 cm. in 1937, and decreased to 49.5 in 1943. The weight of the placenta was 547 Gm. in 1937, and 526 Gm. in 1943. On considering weight differences in the various social groups, one finds in the group of babies of housewives a decrease from 3,330.9 Gm. to 3,063.5 Gm. in weight; 50.3 cm. in 1937 to 49.7 cm. in 1943 in length; and a decrease in placenta weight from 552 Gm. to 521 Gm. In the factory workers, the most underprivileged group in Italy, the weight of the newborn babies reached a low of 2,955.6 Gm. in 1943, as compared with 3,142.5 Gm. in 1937. The length of the babies showed a decrease from 49.6 cm. to 49.2 cm., and the weight of the placenta was reduced to 517 Gm., as compared with the average weight of 541 Gm. in 1937. In the rural districts, the decrease was less spectacular. From an average weight of 3,197 Gm. in 1937, there was a drop to an average of 3,077 Gm. in 1943. From a length of 50 cm., there was a decrease to 49.6 cm., and the weight of the placenta decreased to 528 Gm. from the average 538 Gm. in 1937.

Conclusion: A definite reduction of the length and weight of the fetus, and of the weight of the placenta, which—although showing some differences in favor of the babies of women in rural districts, and a maximum drop in the group of factory workers—is equally noted in the population as a whole, and must therefore be credited to the deterioration of nutrition and emotional strains associated with war.

GEMMA BARZILAI.

Mustakallio, M. J.: On Congenital Sincipital Encephalocele and Its Treatment, With Special Reference to the Structure of the Wall, *Ann. Chirurg. et Gynec. Fenniac* 35: Supplement 2, 1946.

A monograph on the subject of congenital encephaloceles is presented. The literature on the subject, going back as far as the early part of the eighteenth century is covered in detail. Four cases of sincipital encephalocele, all of which were operated and all of which recovered, are then reported. Two were female infants; one three weeks old, and the other seven months old. The other two were a male of 17 years and a female 20 years of age. The symptoms, differential diagnosis, prognosis, and treatment of the condition are then discussed. It is stated that Dandy felt that operation should be postponed until the infant was one year old. However, the results shown by the author in the two infants operated would tend to contradict this.

A detailed study was made of the tissue removed from three of the four cases and anyone interested in this subject would be well advised to refer to this section of the monograph. Finally, in discussing the etiology the author states that, inasmuch as there have been several reports of two or even three cases in the same family, "we must assume that some endogenic factor does exist."

HERBERT J. SIMON.

Nelson, T. Y.: Intracranial Damage in the Newly Born, *M. J. Australia* 1: 268, 1947.

The author wishes to stress the group of cases in which the intracranial damage is so great and the symptoms are so severe that the question of survival is in doubt. The subdural type of hemorrhage is the most frequent and the intracerebral the most infrequent. The various signs and symptoms referable to the different types of intracranial hemorrhage are described. A detailed description of subdural hemorrhage is given as well as means of substantiating this diagnosis.

Early diagnosis and appropriate treatment are essential if the baby is to survive. The author feels that if the presence of blood in the subdural space can be established, the blood should be evacuated as early and as completely as possible.

WILLIAM BERMAN.

Maternal Vitamin A Intake and Ocular Abnormalities in the Offspring,* *Nutrition Rev.* 5: 89, 1947.

The eyes of young, born of rats markedly deficient in vitamin A, show a variety of major anatomic defects and distortions. For these to appear, the maternal serum vitamin A must be one-tenth normal or less; a level at which 25 per cent of the mothers die, fetal resorption is common, and normal birth impossible. At slightly higher levels the eyes show no change whatever. Therefore, it is reasoned that congenital retrolental fibroplasia, which occurs in 8 per cent of infants weighing less than 5 pounds at birth, is probably unrelated to vitamin A deficiency.

IRVING L. FRANK.

Fukas, Von M.: Streptococcal Sepsis of the Newborn From Mastitis in the Pregnant Mother, *Gynaecologia* 123: 53-57, 1947.

Fukas, of Athens, reports an unusual case where a normal male infant was delivered without maternal complications. The baby was apparently in excellent health until three days of age, and ultimately died of streptococcal septicemia. Autopsy confirmed the diagnosis. The mother had suffered from serious mastitis of the left breast for two months prior to delivery. The author was of the opinion that the portal of entrance to the baby was via hematogenous transmission of streptococci in utero, and that the spread of infection occurred in the baby when the antibodies from the mother had been overcome by the overwhelming infection. The placenta was negative to histologic study.

C. E. FOLSOME.

*This is a review article, based on papers of:

1. Warnaky, J., and Schraffenberger, E.: *Proc. Soc. Exper. Biol. & Med.* 57: 49, 1944.
2. Jackson, B., and Kinsey, V. E.: *Am. J. Ophth.* 29: 1234, 1946.

Pregnancy

Belvederi and Morano: Ophthalmosecopy Study of the Eyeground in Pregnancy, Riv. ital. di ginec. 28: 3, 1945.

Belvederi and Morano of the Medical School of Bologna studied retina changes in 142 cases of normal and impaired pregnancies. They found venous hyperemia, retinal vessel spasms, retinal edema, and cottonwool exudate, hemorrhages, macular stars, detachment of the retina, and amaurosis.

They discuss the relationship of those ocular signs and symptoms to findings in cases of pregnancy showing no other pathologic change, in cases associated with renal diseases, or associated with toxic changes.

In cases of otherwise normal pregnancy, venous hyperemia was present in 36 per cent, retinal spasm in 38 per cent, edema in 30 per cent, and retinal stars in 4 per cent of the cases.

In pre-eclampsia, 22 per cent of the cases showed normal eyegrounds; 44 per cent showed venous hyperemia; 38 per cent, retinal spasm; 51 per cent, retinal edema; 15 per cent, retinal stars; 9 per cent hemorrhages; 2 per cent, detachment of the retina.

In cases of renal disease in pregnancy, the eyeground was normal in 37 per cent, there was venous hyperemia in 62 per cent of the cases. Retinal arterial spasm was present in 25 per cent of the cases, retinal edema in 50 per cent, retinal stars in 37 per cent, retinal hemorrhages in 12 per cent.

In cases with severe eclampsia, the eyeground was normal only in 15 per cent of the cases, venous hyperemia was present in 47 per cent, arterial spasm in 43 per cent, retinal edema in 75 per cent, outlined macular stars in 43 per cent, retinal hemorrhages in 34 per cent, detachment of the retina in 6 per cent, amaurosis in 9 per cent of the cases.

On the basis of their findings, the authors advocate routine eyeground examinations on all pregnant women, and repeated examinations in all cases associated with more or less obvious symptoms of toxic changes, or of renal diseases.

GEMMA BARZILAI.

Gianaroli, L.: Capillary Fragility in Pregnancy, Riv. ital. di ginec. 28: 225, 1945.

Studies conducted during wartime by Gianaroli on women at various stages of gestation indicate that a latent vitamin C deficiency was present throughout among pregnant women in the obstetric department of the Medical School in Bologna.

Vitamin C deficiency was evaluated indirectly by approaching capillary fragility. This was done by Cianei's method, that consists in counting the petechiae appearing at bend of elbow, following the application of a suction bell.

During pregnancy and during puerperium, abnormal capillary fragility was demonstrated. It was, however, readily lowered by oral supply of 200 mg. vitamin C daily for seven consecutive days, while a much higher dose was requested to reduce capillary fragility during the puerperium. This shows that in the puerperium there was a higher degree of vitamin C reserve deficiency.

The result of this evaluation of latent vitamin C deficiency through demonstration of capillary fragility parallels findings by Maciotta in earlier research in the same medical school in which vitamin C content of blood and urine was measured in different stages of gestation.

GEMMA BARZILAI.

Toxemia

Umberto, Bracale: Blood and Bone Marrow Disorders Associated With Eclampsia, Arch. di obstet. e ginec. 51: 245, 1947.

In a series of 21 pregnant women, with eclampsia, blood and bone marrow elements were studied. In the peripheral blood, erythrocytes, hemoglobin, and lymphocytes appeared reduced in number, while leucocytes were numerically increased.

In the bone marrow that was obtained by puncture of the sternum, anisocytosis, microcytosis, and macrocytosis were present in the elements of the red series. Hemohistioblasts were increased, and the red and white cell index shifted toward the latter. Myelocytes were definitely increased. As a whole the blood picture revealed alterations in both red and white elements.

GEMMA BARZILAI.

Correspondence

Induction of Labor

To the Editor:

I have read with great interest the report of the discussion on the induction of labor which took place at the Chicago Gynecological Society in November, 1946, and was published in the JOURNAL in September, 1947 (p. 496).

Most British obstetricians will agree with the general conclusions therein, but there is one comment I should like to make on the methods advocated for inducing premature labor.

As Dieckmann and McCready state in their article, the Drew-Smythe catheter is used extensively in British hospitals, and indeed it is the almost universal method of choice. Bags, bougies, etc., are now rarely used, and many of us in this country have long been surprised at the retention of these cumbersome and dangerous instruments by American obstetricians. The reluctance to adopt the catheter method is also curiously conservative. This method carries the great advantage of leaving the forewaters, and consequently the uterine bacteriologic barrier, intact, and has drastically reduced the incidence of infection. As Dieckmann says, labor does not ensue immediately in all, but it does in the great majority of cases, and in any event the procedure may be repeated twice, or even three times.

Simultaneous stimulation with a complete medical induction is a useful reinforcement, and the danger of hemorrhage from damage to the placenta is negligible in careful hands.

ALBERT DAVIS.

93 HARLEY STREET,
LONDON, DEC. 31, 1947.

Drainage of a Hydrocephalic Head

To the Editor:

D. N. Danforth (AM. J. OBST. & GYNEC. 54: 694-695, 1947) presents a modification of the procedure mentioned by Stander for decompressing and draining a hydrocephalic head in a breech presentation. Still another slight modification, available when the spinal canal is opened in the cervical region, consists in using a metallic catheter for passage into the distended ventricles. This variation permits easy collection of the fluids, so that it may be measured for the record.

When there is a spina bifida, as so often happens, a metallic or stiff silk catheter, depending upon the location of the defect, may be passed through the defect in the vertebral arches. Moreover, when the hydrocephalic head presents by the vertex, its fluid contents may be easily drained through a regular abdominal paracentesis trocar passed through an open suture under sight or touch.

These procedures have been employed for many years and have greatly simplified the management of labor complicated by cephalopelvic disproportion on the basis of hydrocephalus, but are rarely mentioned in standard textbooks. They are so much simpler than the classic techniques that their general adoption would seem indicated.

E. D. PLASS, M.D.

IOWA CITY, IOWA
Nov. 3, 1947

Screw Type Cervical Cannula

To the Editor:

I have read, with much interest, the letter of Dr. Paul Titus which appeared in your June (1947) issue; also, the discussion in the November issue.

As one who, for a number of years, has been especially interested in the serew-thread-tip eannula, I was greatly interested in Dr. Titus' remarks, advising against its use.

I should like, very much, to know whether this opinion is based upon theoretical considerations—or whether Dr. Titus has actually had unfavorable experiences with this type of cannula.

I ask this question because I have used this type of cannula over a period of many years and have followed through the results—not only following the examination but also after delivery; this observation covering a number of years. To date, I have not found any unfavorable results from the use of this instrument. Neither have I had one report of any specific ease of injury or disturbance following its use.

If, however, definite cases of injury have been observed, they should be specifically and scientifically reported. It is for this reason that I ask the definite question.

I receive frequent requests for information concerning this technique, and I should like to be specific and accurate in my replies.

The observations and experiences of Dr. Titus—and of others who have used this technique—would be greatly appreciated.

A. P. HUDGINS, M.D.

CHARLESTON, W. VA.

Dec. 6, 1947

Hysterosalpingography—Reply by Dr. Bickers

To the Editor:

The discussion relative to the various procedures in current use relative to "Hysterosalpingography" which appeared in the February, June, and November, 1947, issues of your journal has aroused my interest. Specifically I am concerned over the reference of Dr. Titus and Dr. Weisman to the trauma which they have observed incident to the use of the screw type cannula. This instrument, which was introduced several years ago by Dr. A. P. Hudgins, has so greatly facilitated and expedited hysterosalpingography as an office procedure that I am among those who feel that the instrument has real merit, and its place in the study of human sterility is an important one.

The serew type cervical eannula has been used by me for 112 hysterosalpingographys on 104 patients. In each case the eannula was removed immediately after the x-ray study was completed, and in no case was there any bleeding following the removal. This would seem to indicate that there was little trauma associated with its use. Indeed, it is my impression that this instrument produces less trauma than the tenaeulum which is necessary when one uses the conventional type of cannula. In checking the records on these patients hurriedly I have not been impressed with any increased incidence of cervical erosion nor chronic endocervicitis following the use of this eannula. The ease with which it can be used, the minimum discomfort to the patient, the vastly improved uterine filling and the complete absence of any evidence of trauma to the cervix would seem to permit unqualified recommendation of its use.

WILLIAM BICKERS, M.D.

RICHMOND, VA.

Dec. 28, 1947

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted in Washington, D. C., by the American Board of Obstetrics and Gynecology from Sunday, May 16, through Saturday, May 22, 1948. The Shoreham Hotel in Washington will be the headquarters. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Shoreham Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 1, 1948.

Candidates in military service are requested to keep the Secretary's Office informed of any change in address.

Applications are now being and will be received until November 1, 1948, for the 1949 examinations. For further information and application blanks, address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.
Secretary.

Notice to Diplomates

American Board of Obstetrics and Gynecology, Inc.

The forthcoming fourth edition of the Directory of Medical Specialists plans to designate by appropriate abbreviations whether Diplomates of the above Board practice both branches of the specialty or major in one or the other. The letters OG will be used to indicate combination of practice in both branches, the letter O that the Diplomate majors in obstetrics, and the letter G that he majors in gynecology.

Diplomates who have not already notified the Directory Publication office on this matter in making their biographic returns should communicate with the Directory of Medical Specialists, 210 East Ohio Street, Chicago, Illinois.

PAUL TITUS, M.D.
Secretary.

Erratum

In the article by Lois A. Day, Robert D. Mussey, and Robert W. DeVoe, entitled "The Intrauterine Pack in the Management of Postpartum Hemorrhage," in the February issue of the JOURNAL, on page 234, in the third line above Table II, "276 patients" should read, "267 patients."

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*Fifty-Eighth Annual Meeting
Hot Springs, Va., Sept. 4 to 6, 1947*

PRESIDENTIAL ADDRESS*

Our Heritage and Our Stewardship

A. D. CAMPBELL, M.D., MONTREAL, QUEBEC

THE great honor you have bestowed on me brings with it a sense of pride, which I can assure you is shared by my Canadian colleagues.

The recent catastrophe which has engulfed the world has amply shown how community spirit and common interests can dispel any chauvinism that might otherwise be so easily fostered on either side of the invisible line which divides (but does not separate) us as neighbors. Since our two countries derive their traditions from the same stem, it is but natural that they should have much in common. While our political and social views on this side of the Atlantic are somewhat different from those of the parent stock from which we grew, yet our perspective, our ideals, and ethics are identical. In medicine, all English-speaking countries have a common heritage of which they are, or should be, justly proud.

The gavel, symbolizing as it does so much of the tradition of our Association, is fashioned, as you know, from the home of Ephraim McDowell, who, by his epoch-making operation on Jane Crawford, became our Patron Saint. In a relatively short space of time it has witnessed changes more startling and more far-reaching than did the "Gold-headed Cane" during the centuries in which it represented the best in the medical profession in England.

As one holds this symbol, one is stirred to the depths by vivid recollections of so many eminent men. It seems that their eyes are upon us, and that hidden in the shadow of the wings, silently disapproving or applauding, they still direct

or even prompt those on our stage. Many of them so famous, many now unhappily forgotten, they are, and I hope always shall be, an inspiration to us.

Our professional ancestors down through the centuries have labored long and lovingly to spin the warp and woof of the tapestry upon which we now record the present-day conception of our ancient discipline.

Throughout history, men of scientific vision have rebelled against the dogmatic learning of their time. Their individuality, independence, and originality were less appreciated by their contemporaries than by posterity which they enriched. Their ideals have more or less determined our course and furnished us with relative values by which we should be able to appreciate our opportunities. Even in our time we have known great men whose accomplishments have revealed their inestimable value to mankind. Unfortunately, we are living too close to these achievements to comprehend fully the magnitude of their endeavors. Let us consider it a divine privilege to have been "matched with this hour," to have read original articles written by these men; to have heard their voices from the platform; to have exchanged greetings with them.

It would be unfair not to remember, along with these outstanding figures, the names of the great many who came close to their goal, but, because of circumstances, failed to gain the last step to find the one vital link. Had Lady Luck lent her assistance, or merely smiled upon their efforts, many now forgotten would doubtless rank among the immortals.

Though much of early medicine seems now to be irrelevant, reference to certain historical pioneers should sharpen our interest and provide a living inspiration. The environments and circumstances in which these men were born and worked serve to emphasize the boundless scope for progress afforded us by the present. It would seem ungrateful and ungenerous on our part if we were to allow the incredible advances made during recent years in our profession to blind us to the debt we owe to our predecessors, from whom we have inherited a goodly store of our scientific possessions. Further, it is our responsibility to impart this princely legacy to the present generation and to transmit it to posterity intact—nay, even augmented.

Has not the present position of medicine been the result of a certain series of achievements frustrated by misinterpretations of contemporary thought, but with it all, gradually shaping towards a form of which we are experiencing a mere glimpse? If medicine were articulate, it would justly say as did Tennyson's Ulysses:

I am a part of all that I have met;
Yet all experience is an arch wherethro'
Gleams that untravell'd world whose margins fade
Forever and forever when I move.

Professor Edward Dunster in addressing the New York Academy of Medicine in 1872 observed: "Progress, in any field, parallels the mental inclination and degree of learning of civilization. Our accumulated knowledge gives us a vantage point from which to look back, analyse the past, and reveal its errors." We should be mindful of our successors, for, in their turn, they will undoubtedly recognize in our concepts certain absurdities as we do now so clearly discern those in our ancestors.

Somewhat like the life of nations, medicine has had its periods in which it produced brilliant philosophical and scientific men who practised with sincerity and extraordinary ardor. Such times have, unfortunately, been followed by periods of relative hibernation.

While a study of the cycles of advance and recession is interesting, their fluctuations are difficult to explain. It would seem, however, that universal upheavals tend to reanimate the dormant and awaken the more curious to research, with the result that literature and science have thus often been enriched. Paradoxical as it may appear—the greater the carnage, the more outstanding the advance. The discovery of insulin followed close in the wake of World War I, while World War II gave impetus to an embryonic scientific observation that glorified the humble mold.

Of all the impediments to progress in the past, the blind or slavish adherence to authority and custom has been the greatest. Credulity and superstition have been the means of upholding and spreading error. But this is largely dependent upon "the conditions of the time, the prevailing education, and the degree to which customs, traditions, superstitions, and metaphysical systems were ingrained."

It must not be thought that such adherence is limited to the ignorant and uneducated, for as Sir Thomas Browne (himself reputed to be a believer in witchcraft, though not in alchemy and astrology) observed: "Credulity, though a weakness of the intellect and more discoverable in vulgar heads, yet hath it sometimes fallen upon wiser brains and great advanceers of truth."

In order that new thought may be adopted by the masses, it must first be preceded by a general enlightenment such as may prepare the soil to cherish and foster the acorn which at its maturity will, it is hoped, overshadow and blight the scrubby and useless undergrowth of conventional or time-honored practices.

The old may continue, but, like the new, must stand the test of truth, as only the rational eventually dominates.

It would be an interesting theme to recount the developments in the many aspects of the treatment of puerperal infection since 1773. It was in this year that Charles White of Manchester formulated the present-day conception of asepsis in the prevention of puerperal fever and outlined the care of those so stricken. It would appear that the discoveries of Pasteur and Lister were required to dislodge the ingrained conception that childbed fever was unavoidable or purely the unfriendly act of God. Though the indomitable Lawson Tait held opinions contrary to Pasteur and Lister, nevertheless, these prepared the way for his adoption of the principles of housewifely soap and plenty of hot water, enunciated by White. William Mayo expressed the opinion of modern surgery when he stated: "The cavities of the body were a sealed book until the father of abdominal surgery, Lawson Tait, and our own Joseph Price, carried the sense of sight into the abdominal cavity."

It is not my intention to epitomize chronologically medical history, but rather to comment upon certain characteristics of a few men who have directly

or even indirectly contributed to its existing pattern. Their ideals, their personalities, and, it would seem in some instances, their very faces belong to our history.

Hippocrates clearly saw that the accumulation over the centuries of legends, theories, fancies, and mysticism upon which ancient medicine was based was untenable. He therefore conceived a more logical philosophy and one which appealed to reason. Characteristically a Greek, he was an observer and logician rather than a scientific investigator. He emphasized the rules and regulations regarding cleanliness and set forth certain requirements for the physician's appearance, state of health and attire, as well as those for his conduct.

As the civilization of Greece declined, so did the doctrine and teachings of the Father of Medicine become dissipated. Rome, however, gained ascendancy and with this upsurge, Galen, admittedly a master physiologist and a convincing teacher, was to assume in the new Empire the mantle of Hippocrates. It is true that his ideas were in certain respects at variance with those of Hippocrates, for this approach was entirely different, but the fact that he himself was a Greek and that he referred to the more ancient Greek medicine, kept the embers of the earlier philosophy from being smothered to extinction beneath the intellectually dank atmosphere of the Dark Ages.

Physicians of learning throughout the centuries have recounted the achievements of their predecessors. Linaere revived the teachings of Greek medicine. As Osler remarked—"He brought Harvey back to Galen and Sydenham back to Hippocrates." Similarly, Francis Adams and Littré in the nineteenth century, translating the works of Hippocrates, revived an interest in the ancients. The same is certainly true of our revered Sir William Osler, physician, scholar, and humanist, who not only studied his ancient favorites with loving appreciation, but also accumulated a priceless library in which a student may discover the whole history of the medical discipline and may gaze with awe at precious first editions of many of the classics of the profession.

The intellectual tyranny exercised by the Ancients, the Church, and by the religious sects and orders in medieval days, is from our point of view almost beyond belief. Midwifery was licensed only by the Church. Few, even though relatively enlightened, could display such independence as to defy this tyranny or to dissipate the aura which hovered around the very name of Galen or the Church. Fortunately, however, there were those who put into practice the method of observation and induction advanced by Francis Bacon, whom Abraham Cowley, himself a physician, eulogized—"Bacon, like Moses, led us forth at last."

Harvey, in his rebellion against religious thought, gave evidence of his reckless courage. To quote his own words he "felt in some sort criminal to call in question doctrines which had descended through a long succession of ages and carried the authority of the Ancients; but he appealed unto Nature, that bowed to no Antiquity, and a still higher authority than the Ancients." Harvey, though usually remembered as an experimental physiologist, extended his studies to embryology, medicine, surgery, gynecology, and midwifery. In this later

connection, it is noteworthy that the first original work in midwifery, published in England in 1653, was written by him.

The temperament and behavior of von Hohenheim (Paracelsus) was probably a reaction against irreconcilable opposition and frustration by the suave academicians and bombastic arrogant clinicians of his time. His ruthless attitude seems to have been necessary in attracting attention to himself in a hitherto self-sufficient world which was now being awakened by the dawn of the Renaissance. His independence and originality were further demonstrated, when he insisted on lecturing and writing in the vernacular. Some 200 years elapsed before Dr. Cullen, one of Dr. William Hunter's teachers, similarly deviated from custom by delivering his lectures in English.

Of an opposite disposition was Andreas Vesalius, born in Brussels, keen and scientific by temperament, taciturn of manner, and verging on the melancholic, he made his appearance in Padua to force a breach in the ramparts of accepted medical thought. Had he not been born into a family with medical tradition, he might have been found within the high walls of some remote monastery, a pious monk rather than a pioneer in medical science. In Vesalius was born a passion and a talent for dissection which he regarded as an art and so meticulously performed. Deep in his thoughts, at the risk of his life, he was wont to stroll through the cemeteries or even wait patiently by the executioner's gibbet for an opportunity to seize a body for his beloved purpose. Science lost a pioneer and one of its greatest investigators when, at the age of 29 years, too harassed by his critics and jealous contemporaries, he voluntarily and abruptly discontinued medicine.

Percival Willoughby, a conservative, practical, and modest obstetrician, represented his period. He scorned secrecy and depreciated the erotechet and many of the then current practices of midwifery. Since he felt that he had very little to offer to replace existing customs, his publications were few. Fortunately, however, his notes were preserved and published posthumously, which furnishes us with the most authentic and valuable document on midwifery in the seventeenth century.

Perhaps few realize that clinical instruction, as we know it, dates from Archibald Pitcairne, born in Edinburgh in 1652. Much neglected in history, he was a rare Scotsman of strong character, a poet, a mathematician, and a scholar. For some time a professor in Leyden, he returned to his own city to lay the foundation of bedside teaching as we know it. Like Sydenham, he insisted on strictly scientific methods. Further, like Sydenham, he conceived that Nature lies concealed and that the more sought after, the further she recedes. Among his professional offspring were such eminent physicians as Richard Mead and Boerhaave of Leyden. From his school in Edinburgh came the men who founded McGill University, Laval (now the University of Montreal), and the University of Pennsylvania.

An earlier hero, Ambroise Paré, was a notable example of versatility and resourcefulness. On more than one occasion he performed the different offices of physician, apothecary, surgeon, and cook. On returning from the German

Campaign in 1552, at the Siege of Danvilliers, Paré amputated an officer's leg by his newly devised method, using the ligature instead of hot irons to check hemorrhage—"I dressed him, God healed him." Following this experience, he extended the use of the ligature to arrest hemorrhage in circumstances other than amputation. Only after some twelve years of experience with ligatures did he advise his readers to forgo completely the use of cautery. Curiously enough in 1557, Paré, observing swarms of blowflies on the battlefield, remarked—"I think they were enough to cause the plague where they settled." Was this not the first reference to flies as conveyers of infection?

Everyone knows of the experimental work of that greatest of physiologists, an American, William Beaumont. It was of him that Osler said—"His work remains a model of patient, persevering investigation, experiment and research, and the highest praise we can give him is to say that he lived up to and fulfilled the ideals with which he set out, and which he expressed when he said: 'Truth, like beauty, is 'when unadorned, adorned the most' and, in prosecuting these experiments and inquiries, I believe I have been guided by its light.'" This army physician, stationed on the unfriendly shores of Lake Superior following the War of 1812, though equipped with no special training or technical apparatus, but animated by the spirit of inquiry, seized the opportunity of observing the functions of the stomach in the case of Alexis St. Martin whose abdomen was torn open by gunshot. The recorded observations of this natural physiologist were published, read, and forgotten while academicians still theorized. His observations were later used as a springboard for those engaging in investigations of the functions of the stomach.

Similarly, had not Mrs. Merrill been tossed from her horse, Marion Sims might never have made his monumental contribution to the repair of vesicovaginal fistula.

In like manner, we should, as gynecologists, pay tribute to one Henry Krohn for his keen inquiring mind. We would be well advised to copy the example of Dr. Krohn, similarly recording our observations of various phenomena which as yet have not been clearly explained. Though a relatively obscure London practitioner, he maintained that all unusual phenomena should be published for the edification of fellow practitioners. In 1791, he observed a curious phenomenon in a woman with child. From his description of the patient and his clinical findings, one would at once surmise an abdominal pregnancy. A postmortem was performed and his diagnosis confirmed. His general deductions are interesting, and his queries have not as yet been answered.

The quiet Scottish lad, John Hunter, direct from the cabinet maker's shop, came as a mechanic to his brother, William, then enjoying a selected practice in London. John, who educated himself, became the greatest of clinicians, of surgeons, and of teachers. He studied various physiological phenomena in mammals, birds, and bees; he dissected and mounted thousands of comparative as well as human anatomic specimens for the benefit of those who followed. His anatomic work was the basis of the museum of the Royal College of Surgeons which, alas, was destroyed by a German raid in the recent world war. Hunter was ever cautious of confounding fact and hypothesis. To quote his biographer

—“He had never read Bacon, but his mode of studying Nature was as strictly Baconian as if he had.” Though a prodigious worker, he found time for the company of such friends as Joshua Reynolds, Sam Johnson, and David Garriek. John Hunter serves as an example of achievement through industry, imagination and deductive reasoning.

It may not be inappropriate here to recount a statement which Hunter is said to have made: “My motive was in the first place to serve the hospital, and in the second to diffuse the knowledge of my art, that all might be partakers of it; this, indeed, is the highest office in which a surgeon can be employed; for when considered as a man qualified only to dress a sore or perform a common operation, and perhaps not all of those that may be considered common, he cannot be esteemed an ornament to his profession.”

Jenner was one of those who realized the importance of “the courage of patience.” His observations extended over a decade before he was sufficiently convinced to publish his conclusions. It is particularly worthy of note that though his country was at war with Napoleon, Jenner demonstrated his chivalrous and humanitarian nature by sending Woodville, his assistant, to Paris to control the epidemic of smallpox. Many of you will no doubt recall the simple inscription on the monument which stands on a hillside at Boulogne: “Edward Jenner-La France Reconnaissante.” We can say with confidence of Jenner and Hunter as did W. W. Keen say of Lister: “His name belongs to no age and no country, but to humanity.”

We are particularly interested in Hunterian times, for Morgan, Shippen, Physick, and Rush were the ambassadors who transplanted the ideas of this era to America.

As events recede, it is difficult to estimate the influence upon physicians of contemporary associates other than those directly immersed in their own field. From time to time, by interchanges between professions, many new scientific ideas have undoubtedly been introduced into medical philosophy.

The catholicity of interest displayed by Hunter is exemplified at an earlier date by Sir Christopher Wren, the architect of St. Paul's Cathedral, who knew something of physiology. He illustrated the findings of Willis, and endeavored to devise a means of recording blood pressure. He was probably the pioneer in transferring blood from one individual to another.

Many of those who assisted in the building of medicine did so through their contribution to the general development and spread of knowledge. We are proud of these men, “truants of medicine” as Lord Moyrhan described them, who forsook their original calling to become disciples of science, literature, law, art, and government. While medicine owes much to the humanities, many there were also who attained the highest rank in the “republic of letters,” who owe their understanding of nature and philosophy of life to their early training in physic. In this connection we recall the names of Schiller, Rabelais, Goldsmith, Keats. On this side of the water the immortals, Oliver Wendell Holmes, Sir William Osler, and his disciple, John McRae, throughout their lives claimed a dual interest in literature as well as in their chosen profession of medicine.

We should not permit ourselves to be engulfed in the tides of current ideas. Rudolf Virchow, the father of modern pathology, stoutly maintained that it was mischievous to teach hypothesis which still remained in a speculative stage. Many there are who seize upon the most recent laboratory findings and at once adopt a form of treatment based on their particular interpretation of unproved statements. These "drop the bone for the shadow." Our task as clinicians should be the study of life and human nature, that we may better understand how to apply advances in order to accomplish our common aim of relieving pain and discomfort and of postponing death.

It is regrettable that over the years there should be such an accumulation of medical literature of which a considerable portion is of relatively little importance, much of it tending to increase misunderstanding or add confusion. We must remember that such writings are not like smoke letters in the sky, but are ineradicable and indelible. As Horace observed: "You may destroy what you have not published; but the word once uttered cannot be recalled." What is written is as lasting as civilization, exposed to the endorsement or questioning of generations to come, by which we will be judged as individuals or an era. Let us look well to the pen!

James B. Conant, in addressing the Graduating Class of 1945, McGill University, made it clear—"To be able to add to knowledge the investigator must first be familiar with what is known. Few men have the temperament and the mental qualities which research demands. Research is the intellectual labor of original thinkers and learned men." Is it not inevitable that in former times isolated individuals only had the courage to bring medical teachings and customs under question? Today, every specialist, practitioner, and even the student, regards it as his right and privilege to question the sequence of reasoning in order to understand more clearly the logic of statements. It is, therefore, the lack of proof which stimulates research.

In our teaching, the basic aim of medicine in all universities conforms to a similar pattern with no intention of curbing natural mental endowments. Encouragement is given to those with ability that they may add further to their talents and that their efforts may be rewarded by advancement in some selected sphere. On the other hand, premature concentration on a fancied aspect of medicine should not be encouraged to the detriment of a well-balanced and thorough understanding of basic and essential facts.

Fundamental principles alone are the permanent landmarks of physics. If one is to be a general practitioner, and which of us would forfeit that privilege, he must realize that highly specialized courses, which of necessity are modified from time to time, definitely overshadow the simpler aspects upon which the art of diagnosis and the science of treatment are based. Dr. Rudolph Matas, in his appreciation of William Stewart Halsted, observed: "Nothing so cultivates the noblest human qualities, nothing exalts more the sense of pity, sympathy, and charity than does an intimate knowledge of the causes and consequences of the processes of disease, nothing more stimulates tenderness than the constant contact with suffering and distress."

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PRESIDENTIAL ADDRESS*

Our Heritage and Our Stewardship

A. D. CAMPBELL, M.D., MONTREAL, QUEBEC

THE great honor you have bestowed on me brings with it a sense of pride, which I can assure you is shared by my Canadian colleagues.

The recent catastrophe which has engulfed the world has amply shown how community spirit and common interests can dispel any chauvinism that might otherwise be so easily fostered on either side of the invisible line which divides (but does not separate) us as neighbors. Since our two countries derive their traditions from the same stem, it is but natural that they should have much in common. While our political and social views on this side of the Atlantic are somewhat different from those of the parent stock from which we grew, yet our perspective, our ideals, and ethics are identical. In medicine, all English-speaking countries have a common heritage of which they are, or should be, justly proud.

The gavel, symbolizing as it does so much of the tradition of our Association, is fashioned, as you know, from the home of Ephraim McDowell, who, by his epoch-making operation on Jane Crawford, became our Patron Saint. In a relatively short space of time it has witnessed changes more startling and more far-reaching than did the "Gold-headed Cane" during the centuries in which it represented the best in the medical profession in England.

As one holds this symbol, one is stirred to the depths by vivid recollections of so many eminent men. It seems that their eyes are upon us, and that hidden in the shadow of the wings, silently disapproving or applauding, they still direct

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glorified in song and in story, but the vast majority simply dropped the torch, bright or barely smouldering, for the chance successor, while they themselves, exhausted, silently stumbled into the darkness. Their work went unnoticed; in Sir Thomas Browne's beautiful phrase: "The iniquity of oblivion blindly scattered her poppies," and of their lives of devotion, of constructive thought and sincere endeavor, no memorial remains. It is but right and proper that these simple graves, showing here and there throughout time's boundless cemetery, should be placed hard by those which record achievements widely acclaimed and preserved for posterity. Their deeds shall outlast time. The stoic philosopher came near to the truth when he exclaimed, "Man's true God is the helping of mankind."

These are they who by compounding the best that is in tradition have established the prestige which we now enjoy. Let me hasten to add, however, that prestige is not permanent but withers or dies without continued and earnest endeavor.

We are but the temporary custodians of our great heritage, and if we, and those who follow us, are to retain "a place in the sun" we must cling to the creed of the builders, a creed similar to that suggested by John Ruskin: "When we build, let it be such a work as our descendants will thank us for; and let us think, as we lay stone on stone, that a time is to come when these stones will be held sacred because our hands have touched them, and that men will say as they look upon them, 'See! this our fathers did for us.'"

Even so may it be with any one of us, for what service may lie within our power to perform, we know not. The achievement none can promise for himself, but we can be sure of the aim; and Mordecai's words to Esther may point the destiny of the humblest among us: "Who knoweth whether thou art come to the kingdom for such a time as this?"

1414 DRUMMOND STREET.

Somewhat like the life of nations, medicine has had its periods in which it produced brilliant philosophical and scientific men who practised with sincerity and extraordinary ardor. Such times have, unfortunately, been followed by periods of relative hibernation.

While a study of the cycles of advance and recession is interesting, their fluctuations are difficult to explain. It would seem, however, that universal upheavals tend to reanimate the dormant and awaken the more curious to research, with the result that literature and science have thus often been enriched. Paradoxical as it may appear—the greater the carnage, the more outstanding the advance. The discovery of insulin followed close in the wake of World War I, while World War II gave impetus to an embryonic scientific observation that glorified the humble mold.

Of all the impediments to progress in the past, the blind or slavish adherence to authority and custom has been the greatest. Credulity and superstition have been the means of upholding and spreading error. But this is largely dependent upon “the conditions of the time, the prevailing education, and the degree to which customs, traditions, superstitions, and metaphysical systems were ingrained.”

It must not be thought that such adherence is limited to the ignorant and uneducated, for as Sir Thomas Browne (himself reputed to be a believer in witchcraft, though not in alchemy and astrology) observed: “Credulity, though a weakness of the intellect and more discoverable in vulgar heads, yet hath it sometimes fallen upon wiser brains and great advancers of truth.”

In order that new thought may be adopted by the masses, it must first be preceded by a general enlightenment such as may prepare the soil to cherish and foster the acorn which at its maturity will, it is hoped, overshadow and blight the scrubby and useless undergrowth of conventional or time-honored practices.

The old may continue, but, like the new, must stand the test of truth, as only the rational eventually dominates.

It would be an interesting theme to recount the developments in the many aspects of the treatment of puerperal infection since 1773. It was in this year that Charles White of Manchester formulated the present-day conception of asepsis in the prevention of puerperal fever and outlined the care of those so stricken. It would appear that the discoveries of Pasteur and Lister were required to dislodge the ingrained conception that childbed fever was unavoidable or purely the unfriendly act of God. Though the indomitable Lawson Tait held opinions contrary to Pasteur and Lister, nevertheless, these prepared the way for his adoption of the principles of housewifely soap and plenty of hot water, enunciated by White. William Mayo expressed the opinion of modern surgery when he stated: “The cavities of the body were a sealed book until the father of abdominal surgery, Lawson Tait, and our own Joseph Price, carried the sense of sight into the abdominal cavity.”

It is not my intention to epitomize chronologically medical history, but rather to comment upon certain characteristics of a few men who have directly

TABLE I. CASES OF EXTRAUTERINE PREGNANCY (28 OR MORE WEEKS' GESTATION) REPORTED BY VARIOUS AUTHORS (1933 TO 1947)

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
1. Allen, E.	1933	Full term	Living; died in 8 hours	1,927	Lived	Died	Am. J. Obst. & Gynec. 25: 753-754, 1933.
2. Borngen, H.	1933	7 to 8 months	Dead		Lived	Stillborn	Zentralbl. f. Gynäk. 57: 2968-2971, 1933.
3. Channing-Gaiduk, F.	1933	Full term	Living	3,000	Lived	Lived	Monatsschr. f. Geburtsh. u. Gynäk. 94: 22-28, 1933.
4. Clemente, G.	1933	8 months	Asphyxiated	2,300	Lived	Died	Ann. di ostet. e ginec. 55: 1479-1493, 1933.
5. Fernandes, M.	1933	Full term	Macerated		Died	Stillborn	Arq. de cir. e ortop. 1: 170-178, 1933.
6. Fernandes, M.	1933	Full term	Recently dead		Lived	Stillborn	Arq. de cir. e ortop. 1: 170-178, 1933.
7. Hayes, W. I.	1933	Full term	Lived 24 hours	2,948	Lived	Died	M. J. Australia 2: 17-18, 1933.
8. Mundell, J. J.	1933	Full term	Lived 3 hours; slightly deformed	3,288	Died	Died	M. Ann. District of Columbia 2: 86-90, 1933.
9. Scipiadès, E.	1933	Full term	Living; normal		Lived	Lived	Arch. f. Gynäk. 156: 217-221, 1933.
10. Spackman, W. C.	1933	Full term	Lived 20 minutes		Lived	Died	J. Obst. & Gynaec. Brit. Emp. 40: 1220-1223, 1933.
11. Spackman, W. C.	1933	Full term	Slightly macerated, fully formed	2,494	Died in 5 days	Stillborn	J. Obst. & Gynaec. Brit. Emp. 40: 1220-1223, 1933.
12. Taylor, A. B.	1933	Full-term ruptured tubal pregnancy	Living		Lived	Lived	South African M. J. 7: 437, 1933.
13. Brounagh, W.	1934	2 weeks over term	Died following recent rupture of sac		Lived	Stillborn	Ohio Stato M. J. 30: 823-824, 1934.
14. Colvin, E. D.	1934	7 months	Extremely macerated	28 cm. long 1,940	Lived	Stillborn	Am. J. Obst. & Gynec. 27: 421-428, 1934.
15. Cornell, E. L., and Lash, A. F.	1934	8 months	Living		Lived	Lived	Illinois M. J. 65: 462-466, 1934.
16. Cornell, E. L., and Lash, A. F.	1934	Full term	Lived 18 hours	3,288	Died	Died	Illinois M. J. 65: 462-466, 1934.
17. Cornell, E. L., and Lash, A. F.	1934	Full term	Living	2,381	Lived	Lived	Illinois M. J. 65: 462-466, 1934.
18. Cornell, E. L., and Lash, A. F.	1934	Full term	Living	2,551	Lived	Lived	Illinois M. J. 65: 462-466, 1934.

Case	Author	Year	Full term, size	Living	2267	Lived	Lived	Indian M. Gaz. 69: 61-63, 1934.
20.	Baron	1934	Over term	Died 2 weeks before delivery; well developed	3,150	Lived	Stillborn	Bull. Soc. d'obst. et de gynec. 23: 106-112, 1934.
21.	Holmes, A.	1934	8 months	Lived 9 hours	2,608	Lived	Died	Brit. M. J. 2: 111-113, 1934.
22.	Holt, E. T.	1931	Full term	Macerated	4,139	Lived	Stillborn	Am. J. Obst. & Gynec. 28: 452-454, 1934.
23.	Israel, A., and Jaber, E.	1934	Full term	Dead for 1 month		Lived	Stillborn	Am. Fac. franc. de med. et de pharm. de Beyrouth 3: 119-121, 1934.
24.	Leach, E. B., and McCurich, H. J.	1934	Full term	Macerated, deformed	3,061	Lived	Stillborn	Brit. M. J. 1: 557-558, 1934
25.	MacGregor, T. G.	1934	Full term	Twins: 1 small, macerated; other lived 12 hours		Died	1 died 1 stillborn	West African M. J. 8: 12, 1934.
26.	Margelson, N. J. L., and Ogilvie, D. C.	1934	8 months	Dead		Lived	Stillborn	Brit. M. J. 2: 115, 1934.
27.	Powell	1934	Full term	Living	3,855	Died in 10 hours	Stillborn	J. Kansas M. Soc. 35: 99-102, 1934.
28.	Reamy	1934	7 months	Macerated		Lived	Stillborn	Gynec. & Obst. 9: 440, 1924.
29.	Roxas Villarama	1934	7 months	Lived		Lived	Lived	J. Philippine Islands M. A. 4: 50, 1924.
30.	Sriningsom, H.	1934	Full term; vaginal delivery; intra-uterine pregnancy	Macerated	2,778	Died in 1 day	Stillborn	Malayan M. J. 9: 174, 1934.
31.	Steed, W. A.	1934	Full term	Lived 12 hours	3,033	Lived	Died	Brit. M. J. 2: 62-63, 1934.
32.	Toussay	1934	9 years	Dead: 6 months' development		Lived	Stillborn	Cited by Bland, et al., 1934.
33.	Arndt, E.	1935	12 months	Dead, macerated	1,400	Lived	Stillborn	Gynecologie 34: 481-488, 1935.
34.	Arndt, E.	1935	13 months	Dead, macerated	2,550	Lived	Stillborn	Gynecologie 34: 481-488, 1935.
35.	Arndt, E.	1935	Full term	Well developed, lived 1 day	2,600	Died	Died	Gynecologie 34: 481-488, 1935.
36.	Arndt, E.	1935	Full term	Living	3,000	Died	Lived	Gynecologie 34: 481-488, 1935.
37.	Beagart, H. S.	1935	Full term	Lived 1 day	4,300	Died	Died	Nederl. tijdschr. v. geneesk. 79: 523-524, 1935.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
38. Boogart, H. S.	1935	Full term	Dead		Lived	Stillborn	Nederl. tijdschr. v. geneesk. 79: 523-5231, 1935.
39. Boogart, H. S.	1935	Full term	Dead		Lived	Stillborn	Nederl. tijdschr. v. geneesk. 79: 523-5231, 1935.
40. Cernovic, M. U.	1935	Full term	Dead		Lived	Stillborn	Bratisl. leKar. listy 15: 176, 1935.
41. Daners, H.	1935	17 days over term	Dead	3,700	Died in 19 days	Stillborn	Zentralbl. f. Gynäk. 59: 212-218, 1935.
42. Ejsman, J. R., and Ziegler, E.	1935	Full term	Living	3,232	Lived	Lived	J. A. M. A. 104: 2175-2176, 1935.
43. Ferguson, J. A., and Otis, L. S.	1935	12 months	Well-developed twins. dead	1,730	Lived	Stillborn	Am. J. Obst. & Gynec. 30: 139-141, 1935.
44. Hellman, A. M., and Simon, H. J.	1935	Full term	Living. normal	3,855	Lived	Lived	Am. J. Surg. 29: 403-413, 1935.
45. James, J. E., Jr. and Lafferty, H. D.	1935	7 months	Dead		Lived	Died	Am. J. Obst. & Gynec. 29: 711-714, 1935.
46. James, J. E., Jr., and Lafferty, H. D.	1935	Full term	Dead		Lived	Died	Am. J. Obst. & Gynec. 29: 711-714, 1935.
47. James, J. E., Jr., and Lafferty, H. D.	1935	Full term	Dead		Lived	Died	Am. J. Obst. & Gynec. 29: 711-714, 1935.
48. Longley, E. G.	1935	8½ months	Dead several hours	3,288	Lived	Stillborn	Am. J. Surg. 27: 349-352, 1935.
49. Posner, A. C.	1935	Full-term prolapsed cervix	Living	3,543	Died	Lived	Am. J. Obst. & Gynec. 30: 293-295, 1935.
50. Sarkar, A.	1935	28 weeks	Macerated		Lived	Stillborn	J. Obst. & Gynaec. Brit. Emp. 42: 112-1125, 1935.
51. Stapleton, G.	1935	Full term	Macerated		Lived	Stillborn	Brit. M. J. 1: 879, 1935.
52. Swanson, C. N.	1935	Full term	Dead		Lived	Stillborn	J. Michigan M. Soc. 34: 585-589, 1935.
53. Swanson, C. N.	1935	Full term	Dead		Lived	Stillborn	J. Michigan M. Soc. 34: 585-589, 1935.
54. Swanson, C. N.	1935	Full term	Dead		Lived	Stillborn	J. Michigan M. Soc. 34: 585-589, 1935.
55. Swanson, C. N.	1935	Full term	Living		Lived	Lived	J. Michigan M. Soc. 34: 585-589, 1935.
56. Swanson, C. N.	1935	Full term	Living		Lived	Lived	J. Michigan M. Soc. 34: 585-589, 1935.

No.	Author, C. N.	Year	Full term	Dead	Weight	Survived	Notes
64.	McCormac, C. N.	1935	Full term	Dead		Stillborn	J. Michigan M. Soc. 34: 585-589, 1935.
65.	McCormac, C. N.	1935	Premature	Dead	1,165	Lived	J. Michigan M. Soc. 34: 585-589, 1935.
66.	McCormac, C. N.	1935	Premature	Dead		Lived	J. Michigan M. Soc. 34: 585-589, 1935.
67.	McCormac, C. N.	1935	Premature	Dead		Lived	J. Michigan M. Soc. 34: 585-589, 1935.
68.	McCormac, C. N.	1935	Premature	Dead		Lived	J. Michigan M. Soc. 34: 585-589, 1935.
69.	Zard, M.	1935	2 to 3 weeks before term	Living; deformed	2,033	Lived	Ztschr. f. Kinderh. 57: 505-515, 1935.
70.	Anderson, M. W.	1936	Full term	Dead at birth; believed to be primary abdominal	2,721	Lived	Brit. M. J. 2: 589-590, 1936.
71.	Carney, A. D.	1936	7 months	Dead		Lived	Tri-State M. J. 8: 1664-1665, 1936.
72.	de Silva, A.	1936	Post term	Living	1,501	Lived	Indian M. Gaz. 71: 590-591, 1936.
73.	Douglas, L. H.	1936	8 months	Dead, deformed	1,380	Lived	Nebraska M. J. 21: 338-340, 1936.
74.	Fath, F.	1936	Full term	Lived 12 days	3,400	Lived	München. med. Wchnschr. 83: 92, 93, 1936.
75.	Grosshull, J. P.	1936	12 months	Macerated, deformed		Lived	J. A. M. A. 106: 606-608, 1936.
76.	Krishnan, R. G.	1936	Full term	Living		Lived	Brit. M. J. 1: 795, 1936.
77.	Leandre, M.	1936	8½ months intra-uterine pregnancy	Mummified	2,140	Lived	Bull. Soc. d'obst. et de gynec. 25: 204-205, 1936.
78.	Macerzotti, M.	1936	8 months	Macerated, intra-ligamentous		Lived	Clin. ostet. 38: 651-661, 1936.
79.	Frays, W. M., and Wiersma, J. S.	1936	Full term	Living		Lived	Gemeinsk. tijdschr. v. Nederl. Indie 76: 3427-3436, 1936.
80.	Schmiedel, E. A.	1936	Full term	Dead, well formed	2,835	Lived	Ann. J. Surg. 33: 570-573, 1936.
81.	Wibben, O. S.	1936	Full term; vaginal delivery	Dead; driven through sac of Douglas, ripping uterus from attachments		Lived	Proc. Roy. Soc. Med. 29: 1651-1654, 1936.
82.	Wilson, A. S.	1936	8½ months	Living	2,381	Lived	Proc. Roy. Soc. Med. 29: 1651-1654, 1936.
83.	Wilson, W. N.	1936	Full term, tubal pregnancy	Dead	2,880	Lived	Proc. Roy. Soc. Med. 29: 1651-1654, 1936.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
77. Woods, E. B.	1936	Full term	Living	2,324	Died	Lived	AM. J. OBST. & GYNEC. 32: 155-157, 1936.
78. Bondurant, F.	1937	8½ months	Normal, living; twin to 3½ lb. intrauterine baby that lived 5 days	2,154	Lived	Lived	Illinois M. J. 71: 480-481, 1937.
79. Burke, F. J.	1937	7 months	Macerated, no deformities	2,494	Died	Stillborn	Brit. M. J. 1: 775, 1937.
80. Burke, F. J.	1937	34 weeks	Macerated, talipes equinovarus	2,267	Lived	Stillborn	Brit. M. J. 1: 775, 1937.
81. Crichton, E. C.	1937	Full term	Dead, slightly deformed		Lived	Died	South African M. J. 11: 229-230, 1937.
82. Crichton, E. C.	1937	Full term	Lived for a few minutes		Lived	Died	South African M. J. 11: 229-230, 1937.
83. Crichton, E. C.	1937	Full term	Macerated, no deformity	4,082	Lived	Died	South African M. J. 11: 229-230, 1937.
84. Elsholz	1937	Full term	Normal except clubfooted	3,500	Lived	Lived	Ztschr. f. Geburtsh. u. Gynäk. 115: 489-495, 1937.
85. Eno, E., and Towers, A. E.	1937	Full term	Living, deformed	3,345	Died	Lived	Chinese M. J. 51: 33-40, 1937.
86. Eno, E., and Towers, A. E.	1937	Full term	Lived 6 hours		Lived	Died	Chinese M. J. 51: 33-40, 1937.
87. Friedman, S. L.	1937	7 months	Macerated		Lived	Stillborn	AM. J. OBST. & GYNEC. 33: 683-686, 1937.
88. Hoffman, W. E.	1937	Near term	Lived 12 hours	2,097	Lived	Died	West Virginia M. J. 33: 496-497, 1937.
89. Kariki-Pahwa, R. R. D.	1937	14½ months	Dead for some time	5,443	Lived	Stillborn	Lancet 1: 1228, 1937.
90. Kreis, J.	1937	Full term	Lived, Cesarean delivery		Lived	Lived	Rev. franç. de gynéc. et d'obst. 32: 89-116, 1937.
91. Kyriakis, L.	1937	8 months	Lived 40 hours		Lived	Died	Gatrika chronica (Greek, 1937; abst. Zentralbl. f. Gynäk. 64: 991, 1940.
92. Lailey, W. W.	1937	4 to 5 weeks over term broad ligament pregnancy	Overmature, living, clubfooted	5,017	Lived	Lived	Canad. M. A. J. 36: 67-68, 1937.

	Year	Near term	Living, slight deformity corrected	Weight	Lived	Lived	AM. J. OBST. & GYNEC.
94. MacGregor, A. S.	1937	Near term	Living	2,660	Lived	Lived	1032, 1937.
95. MacGibbon, V.	1937	Full term	Living	1,917	Died in 5 days	Lived	Gynecologia 3: 35-46, 1937.
96. MacMissig, V.	1937	Full term	Dead		Stillborn		Gynecologia 3: 35-46, 1937.
97. McNichol, F. G.	1937	7 months	Normal, living		Lived	Lived	West. J. Surg. 45: 119-133, 1937.
98. Oakes, E.	1937	Near term	Lived 4 hours	3,457	Lived	Died	Rassegna di ostet. e. ginec. 46: 59-73, 1937.
99. Parker, P. E.	1937	Full term	Shrivelled, faint heart beat at 10th month		Lived	Stillborn	J. Tennessee M. A. 30: 163-165, 1937.
100. Rogers, P., and Winterdon, W. R.	1937	40 weeks	Dead		Lived	Stillborn	J. Obst. & Gynec. Brit. Emp. 44: 687-695, 1937.
101. Scherach, W.	1937	Full term, ovarian pregnancy	Living, normal	3,000	Died in 1 day	Lived	Arch. f. Gynäk. 162: 371-378, 1937.
102. Stenningen, R.	1937	Full term	Living	3,200	Lived	Lived	Med. Klin. 33: 1609-1610, 1937.
103. Stool, G.	1937	Full term	Lived 24 hours	2,100	Lived	Died	Nederl. tijdschr. v. geneesk. 81: 1021-1024, 1937.
104. Varner, H. H., and Green, L. Jr.	1937	Full term, tubal pregnancy	Dead		Died	Stillborn	Southwestern Med. 21: 191-196, 1937.
105. Wherry, L. P.	1937	Full term	Lived, clubfooted; only partly outside uterus; previous section scar torn		Lived	Lived	Brit. M. J. 1: 1158, 1937.
106. Gray, P. N.	1938	8 months	Newly dead	1,353	Lived	Stillborn	Minnesota Med. 21: 498-500, 1938.
107. Champion, P. K., and Telford, N. J.	1938	10 months	Macerated	3,855	Lived	Stillborn	AM. J. OBST. & GYNEC. 36: 291-293, 1938.
108. Green, W. D., and Cascardi, R. A.	1938	Full term	Living	2,604	Lived	Lived	AM. J. OBST. & GYNEC. 36: 312-313, 1938.
109. Gainer, C. D., Collins, C., and Brown, H.	1938	7 months	Lived 7 hours, sac ruptured 1 week before birth	1,871	Died	Died	South. M. J. 31: 1278-1280, 1938.
110. Gainer, C. D., Collins, C., and Brown, H.	1938	Full term	Macerated		Lived	Stillborn	South. M. J. 31: 1278-1280, 1938.
111. Gerrard, R. A.	1938	Full term	Macerated		Lived	Stillborn	Clin. J. 67: 116-118, 1938.
112. Hardy	1938	8 months	Calcified, dead 10 years		Lived	Stillborn	Reported by Champion-Tessitore.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
112. Harkness, J., and Bell, F.	1938	Full term	Dead, vertex pres- entation through vagina	3,401	Died	Died	Brit. M. J. 2: 1044, 1938.
113. Hellman, A. M., and Simon, H. J.	1938	Full term	Macerated		Lived	Stillborn	AM. J. OBST. & GYNEC. 35: 289- 294, 1938.
114. Jennings, D., and Hunsucker, W. C.	1938	7 months	Living		Lived	Lived	South. M. & S. J. 100: 585-589, 1938.
115. Kaufman, L. G., Finley, R. K., and King, H. E.	1938	Unknown	Disembowered fetal bones		Died	Stillborn	Ohio State M. J. 34: 525-527, 1938.
116. König, H.	1938	7 months	Lived 12 months	850	Lived	Died	Zentralbl. f. Gynäk. 62: 2322-2326, 1938.
117. Lelling, E.	1938	7 months	Died at birth, deformed	38 cm. long	Died	Died	Zentralbl. f. Gynäk. 62: 2209-2214, 1938.
118. Novey, M. A.	1938	Full term	Greatly macerated		Lived	Stillborn	Surg., Gynec. & Obst. 66: 671-676, 1938.
119. Novey, M. A.	1938	Near term	Dead		Died	Stillborn	Surg., Gynec. & Obst. 66: 671-676, 1938.
120. Novey, M. A.	1938	40 weeks	Large, macerated	3,798	Died	Stillborn	Surg., Gynec. & Obst. 66: 671-676, 1938.
121. Novey, M. A.	1938	Near term	Living, deformed feet	2,494	Lived	Lived	Surg., Gynec. & Obst. 66: 671-676, 1938.
122. Novey, M. A.	1938	Term?	Living, normal	2,693	Lived	Lived	Surg., Gynec. & Obst. 66: 671-676, 1938.
123. Payne, R. H.	1938	14 months	Dead	3,288	Lived	Stillborn	AM. J. OBST. & GYNEC. 36: 693- 697, 1938.
124. Posner, A. C.	1938	10 months	Macerated	2,381	Lived	Stillborn	AM. J. OBST. & GYNEC. 36: 693-697, 1938.
125. Posner, A. C.	1938	7 months	Dead	1,275	Lived	Stillborn	Vida nuova 42: 605-611, 1938.
126. Ramirez Olivella, J., Barroso, L., and Machado, O.	1938	Full term	Living	3,175	Lived	Lived	
127. Ritsema van Eck, C. R.	1938	Full term	Living	3,170	Lived	Lived	Geneesk. tijdschr. v. Nederl. Indie. 78: 1711-1713, 1938.
128. Stabler, F.	1938	Full term	Living, tempo- rarily deformed	2,381	Lived	Lived	Brit. M. J. 1: 779-780, 1938.
129. Tarleton, L.	1938	10 months	Dead, overmature		Lived	Stillborn	Brit. M. J. 2: 569, 1938.

130. Bergenfelz, E.	1939	Full term	Died after 4 hours	2,850	Lived	Died	Acta obst. et gynec. scandinav. 19: 274-289, 1939.
131. Rickop, H. W. F.	1939	Full term	Living	2,494	Lived	Lived	South African M. J. 13: 167-168, 1939.
132. Carlet, P. M.	1939	Full term, tubal rupture at 7 months	Dead	2,381	Lived	Stillborn	
133. Cunningham, J. F.	1939	8 months	Dead	1,105	Lived	Stillborn	Irish J. M. Sc. pp. 846-847, 1939.
134. Cunningham, J. F.	1939	Full term	Living	1,927	Lived	Lived	Irish J. M. Sc. pp. 846-847, 1939.
135. Gifford, J. R.	1939	1 week over term	Died just before operation, ruptured into abdomen through cesarean section scar		Lived	Died	AM. J. Obst. & Gynec. 37: 466-472, 1939.
136. Hains, J. C.	1939	Full term	Living	3,515	Lived	Lived	M. J. Australia 1: 268-269, 1939.
137. Longmire, S., and Palazo, W.	1939	Full term	Dead		Lived	Stillborn	Am. brasil. de gynec. 8: 302-312, 1939.
138. Mathison, A.	1939	26 years	Lithopedion	37 g	Lived	Stillborn	AM. J. Obst. & Gynec. 37: 297-302, 1939.
139. Smyth, G. S., and MacKintosh, R. H.	1939	14 months	Slightly macerated		Lived	Stillborn	South African M. J. 13: 320-321, 1939.
140. Snow, W.	1939	Near term	Lived 5 hours		Lived	Died	Am. J. Roentgenol. 41: 537-540, 1939.
141. Vandevoort, M., and de Tournay, G.	1939	8½ months	Living	2,030	Lived	Lived	Bruxelles-med. 19: 333-338, 1939.
142. Acosta-Soto, H., and Espinola, N. A.	1940	Full term	Living	3,800	Lived	Lived	Acta med. Phillipina 2: 31-36, 1940.
143. Ayres, Netto P., et al.	1940	Full term	Dead several hours			Stillborn	Bot. Soc. de med. e cir de sao Paulo 23: 8-23, 1939.
144. Ayres, Netto P.	1940	Full term	Dead several hours			Stillborn	Bot. Soc. de med. e cir de sao Paulo 23: 8-23, 1939.
145. Bond, A. M., and Casool, N. S.	1940	Full term	Died at delivery; left foot had pierced broad ligament, foot deformed	3,175	Lived	Stillborn	J. Iowa M. Soc. 30: 145-147, 1940.
146. Becker, C.	1940	7 months	Died at birth	1,200	Lived	Died	Zentralbl. f. Gynäk. 64: 2667-1668, 1940.
147. Capelara, V. M.	1940	Full term	Dead		Lived	Stillborn	Rev. med. veterinaria 20: 3119-3121, 1940.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
148. Chung, C. T.	1940	14 months	Dead, well devel- oped, dehydrated	1,980	Lived	Stillborn	Chinese M. J. 57: 184-185, 1940.
149. Elkins, H. B., and Bowdle, R. A.	1940	Full term	Macerated	2,948	Lived	Stillborn	Am. J. Surg. 49: 116-117, 1940.
150. Gavaldon Salamanca, A.	1940				Lived	Died	J. Internat. Coll. Surgeons 3: 271- 272, 1940.
151. Gomez Azcarate, G.	1940	Full term	Living		Lived	Lived	Cir. y. cirujanos 8: 179-190, 1940.
152. Gomez Azcarate, G.	1940	Full term	Living		Lived	Lived	Cir. y. cirujanos 8: 179-190, 1940.
153. Gomez Azcarate, G.	1940	Full term	Living		Lived	Died	Cir. y. cirujanos 8: 179-190, 1940.
154. Gomez Azcarate, G.	1940	Full term	Living		Lived	Died	Cir. y. cirujanos 8: 179-190, 1940.
155. Gomez Azcarate, G.	1940	Full term	Living		Lived	Died	Cir. y. cirujanos 8: 179-190, 1940.
156. Hamblen, N.	1940	Full term	Lived 3 hours	2,324	Lived	Died	West. J. Surg. 48: 310-312, 1940.
157. Leinzinger, E.	1940	Full term	Macerated, de- formed	3,000	Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1506, 1940.
158. Lull, C. B.	1940	7 months	Died at birth		Died in 8 hours	Died	AM. J. OBST. & GYNEC. 40: 194- 202, 1940.
159. Lull, C. B.	1940	7½ months	Macerated		Died in 4 months of T.B.	Stillborn	AM. J. OBST. & GYNEC. 40: 194- 202, 1940.
160. Lull, C. B.	1940	8½ months	Living	2,211	Lived	Lived	AM. J. OBST. & GYNEC. 40: 194- 202, 1940.
161. Nicodemus, R. E., and Carigg, L. G.	1940	7½ months	Died at birth	2,069	Lived	Died	AM. J. OBST. & GYNEC. 39: 153- 154, 1940.
162. Oghi, A.	1940	Full term	Macerated		Died in 36 hours	Stillborn	Senana med. 2: 1311-1313, 1940.
163. von Pallos, K.	1940	Full term	Macerated		Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1052-1061, 1940.
164. von Pallos, K.	1940	14 months	Dead		Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1052-1061, 1940.
165. Richter, W.	1940		No details		Lived	Lived	Zentralbl. f. Gynäk. 64: 1505-1506, 1940.
166. Richter, W.	1940		No details		Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1505-1506, 1940.
167. Richter, W.	1940		No details		Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1505-1506, 1940.
168. Satta Flores, G.	1940	8 months	Lived 24 hours	3,070	Lived	Died	Clin. obstet. 42: 306-313, 1940.
169. Sigwart, W.	1940	8 months	Dead		Lived	Stillborn	Zentralbl. f. Gynäk. 64: 1906-1911, 1940.

170. Singer, E. A. R.	1940	Full term	Dead	3,175	Lived	Stillborn	Brit. M. J. 1: 91, 1940.
171. Fajzabek Jasty, A.	1940	Full term	Macerated	1,700	Lived	Stillborn	Duodecim. 56: 130-163, 1940.
172. Spachino, J. R., and Chappell, M. R.	1940	Full term	Lived 48 hours	3,231	Lived	Died	Ohio State M. J. 36: 520-521, 1940.
173. Tejerna Pathology, Inc., W.	1940	Full term	Living	2,400	Lived	Lived	Bol. Soc. de obst. ginec. 19: 657-669, 1940.
174. Alcock, S. R.	1941	12 months	8 to 9 months' dead fetus		Lived	Stillborn	Calcutta M. J. 38: 301-304, 1941.
175. Langner, E.	1941	Full term	Living	3,500	Died in 1 hr.	Lived	Zentralbl. f. Gynäk. 65: 819-822, 1941.
176. Leach, R. R.	1941	Full term	Lived ½ hour, sac ruptured 22 days earlier after delivery of 5½ pound intrauterine living twin	2,721	Lived	Died	Brit. M. J. 2: 805, 1941.
177. Matcovsky, A.	1941	Full term	Living	3,400	Lived	Lived	Geburtsh. u. Frauenh. 3: 242-246, 1941.
178. Noy de Almeida	1941	Full term	Living	2,270	Lived	Lived	An. brasíl. de ginec. 12: 299-307, 1941.
179. Nicholls, R. R.	1941	10 month ovarian	Living	4,620	Lived	Lived	AM. J. Obst. & Gynec. 42: 341-342, 1941.
180. Renner, M. J.	1941	Full term	Living	3,061	Lived	Lived	J. Kansas M. Soc. 42: 245-247, 1941.
181. Schwarz, M.	1941	Full term	Living		Lived	Lived	Zentralbl. f. Gynäk. 65: 204-209, 1941.
182. Syetor	1941	7 months	Dead	2,340	Lived	Stillborn	Zentralbl. f. Gynäk. 65: 1056-1062, 1941.
183. Torquast, G. W.	1941	3 weeks over term	Living, normal	4,100	Died	Lived	Acta obst. e. gynec. scandinav. 21: 100-102, 1941.
184. Viorita Marcellos, A.	1941	Full term	Living	2,800	Lived	Lived	Revista de dinel. e d'obst. 35: pt. 1, 1-15, 1941.
185. Wentrub, M., and Wentrub, D. L.	1941	7 months	Macerated		Lived	Stillborn	Am. J. Surg. 54: 747-752, 1941.
186. White, R. A.	1941	Full term	Made a few feeble movements	2,267	Lived	Died	North Carolina M. J. 2: 87-92, 1941.
187. Henshaw, W. S., and Strongman, C. R.	1942	7 months	Dead, poorly developed	13 inches long	Lived	Stillborn	Cincinnati J. Med. 23: 477-488, 1942.
188. Lacey, C. F.	1942	8 months tubal, early rupture	Lived	2,381	Lived	Lived	Brit. M. J. 1: 722, 1942.
189. Mortonghy, R., and Menzies, L. J.	1942	Full term	Dead		Died	Stillborn	Radiology 38: 35-38, 1942.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTIER	BABY	
190. Mattingly, D., and Menville, L. J.	1942	Full term	Dead		Lived	Stillborn	Radiology 38: 35-38, 1942.
191. Mattingly, D., and Menville, L. J.	1942	Full term	Normal, living		Lived	Lived	Radiology 38: 35-38, 1942.
192. Mattingly, D., and Menville, L. J.	1942	8 months	Dead		Lived	Stillborn	Radiology 38: 35-38, 1942.
193. Mattingly, D., and Menville, L. J.	1942	7 months	Dead		Lived	Stillborn	Radiology 38: 35-38, 1942.
194. Netto, P.	1942	Full term	Living		Died	Lived	Med. cir. pharm. pp. 455-466, 1942.
195. Schnitze, H.	1942	10 months	Dead.		Lived	Stillborn	Zentralbl. f. Gynäk. 66: 455-468, 1942.
196. Slotover, M. L.	1942	Full term	Macerated		Lived	Stillborn	Brit. M. J. 1: 669, 1942.
197. Wallau, F.	1942	14 days be- fore term, tubal	Living	2,040	Lived	Lived	Zentralbl. f. Gynäk. 66: 1298-1308, 1942.
198. Wide, E. R.	1942	pregnancy	Dead		Lived	Stillborn	Brit. M. J. 1: 916-917, 1946.
199. Hart, S. D.	1943	Full term	Macerated	2.3 kg.	Lived	Stillborn	West. J. Surg. 51: 280-282, 1943.
200. Hudgins, A. P.	1943	7 months	Dead, anencephalic		Lived	Stillborn	South. M. J. 36: 678-680, 1943.
201. Kobak, A. J.	1943	7½ months	Dead, clubfooted	19 cm.	Lived	Stillborn	AM. J. OBST. & GYNEC. 46: 577-579, 1943.
202. Loveless, P. H., and Austin, C. P.	1943	13 months	Macerated	2,523	Lived	Stillborn	Southwest. Med. 27: 301-303, 1943.
203. Lubin, S., and Walt- man, R.	1943	11 months	Macerated	1,190	Lived	Stillborn	Am. J. Surg. 60: 298-300, 1943.
204. Martin, P. J., and Grier, M. E.	1943	8 months	Macerated		Lived	Stillborn	Nebraska M. J. 28: 148-149, 1943.
205. Penick, G.	1943	Full term	Mummified		Lived	Stillborn	J. Oklahoma M. A. 36: 192-195, 1943.
206. Pizarro, J. J.	1943	Full term	Macerated		Lived	Stillborn	Hospital (Rio de Janeiro) 24: 253-272, 1943.
207. Poddar	1943	7 months	Dead	1,757	Lived	Stillborn	Indian M. Gazette 78: 434-436, 1943.
208. Poddar	1943	Term?	Dead	3,175	Lived	Stillborn	Indian M. Gazette 78: 434-436, 1943.
209. Poddar	1943	Full term	Dead, monster		Lived	Stillborn	Indian M. Gazette 78: 434-436, 1943.
210. Rajoo, T. D., and Maddimsetti, H. P.	1943	Term	Lithopedion, died 5 mo. after rupture of sac		Lived	Stillborn	Indian M. Gazette 78: 433-434, 1943.

211. Schupp, K. L.	1943	Full term	Living	2,833	Lived	Lived	West, J. Surg. 51: 191-193, 1943.
212. Cannon, D., and Heller, E. L.	1943	7 months' tubal pregnancy; delivered at autopsy of mother who died of generalized T.B.			Died	Stillborn	Am. J. Obst. & Gynec. 45: 345-350, 1943.
213. Strumpf, I. J.	1943	Full term	Living, normal		Lived	Lived	Am. J. Obst. & Gynec. 45: 350-353, 1943.
214. Thorey, R. C.	1943	34 weeks	Macerated		Lived	Stillborn	J. Obst. & Gynec. Brit. Emp. 50: 189-195, 1943.
215. Archer, B. V.	1944	Full term	Well developed, lived 4 days	2,778	Died	Died	M. Bull. Bombay 12: 1-5, 1944.
216. Benoit, N.	1944	12 months	Dead		Died	Stillborn	Chinese M. J. 62: 197-198, 1944.
217. Chavira, R.	1944	Full term	Normal, living	2,000	Lived	Lived	Obst. y ginec. latino-am. 2: 213-216, 1944.
218. Benson, H. L., Jr., and Henderson, W. C.	1944	8 months	Retained 8 years		Lived	Stillborn	Am. J. Surg. 63: 257-258, 1944.
219. Diphda, S. A.	1944	Full term	Lithopedion	4,195	Lived	Stillborn	Am. J. Surg. 63: 102-104, 1944.
220. Gardner, A. R., and Middlebrook, G.	1944	Full term	Living	2,239	Lived	Lived 4½ months	Am. J. Surg. 66: 161-167, 1944.
221. Grady, M. W., and Polayco, S. R.	1944	Full term	Macerated		Lived	Stillborn	Am. J. Obst. & Gynec. 48: 379-386, 1944.
222. Lee, A. V.	1944	Full term	Lived 2 hours, delivered		Lived	Died	Chinese M. J. 62: 383-387, 1944.
223. Pearson, J. W., Jr., and Parks, J.	1944	7 months	Lived 12 hours	1,333	Lived	Died	Am. J. Obst. & Gynec. 47: 127-129, 1944.
224. Pump, K. K.	1944	12 months	Dead	2,267	Lived	Stillborn	Bull. Vancouver M. A. 20: 110-111, 1944.
225. Greene, G. G.	1945	Full term	Large, macerated		Lived	Stillborn	South. M. J. 38: 747-752, 1945.
226. Greene, G. G.	1945	7 months	Macerated		Lived	Stillborn	South. M. J. 38: 747-752, 1945.
227. Greene, G. G.	1945	Full term	Died at birth		Lived	Died	South. M. J. 38: 747-752, 1945.
228. Morgan, R. G., and Koehl, N. L.	1945	About 8 months	Lived 1 hour		Lived	Died	Brit. M. J. 2: 640, 1945.
229. Bass, M. J.	1945	Full term	Living, normal	2,324	Lived	Lived	J. Florida M. A. 31: 475-476, 1945.
230. Seltah, L. G., and Hall, W. C. O.	1945	Full term, see tubal, secondary opening in- to birth canal	Dead, well developed	1,389	Died	Stillborn	J. Obst. & Gynec. Brit. Emp. 52: 71-74, 1945.
231. Seltah, P. O.	1945	Near term	Died 1 week before operation, macerated	2,724	Lived	Stillborn	Urol. & Gynec. Rev. 49: 338-340, 1945.

TABLE I—CONT'D

AUTHOR	RE- PORTED	DURATION OF PREGNANCY	STATUS OF FETUS	WEIGHT (GM.)	RESULT		REFERENCE
					MOTHER	BABY	
232. Armand, M. F., and Sam, F. G.	1946	Full term	Normal, well formed	3,401	Lived	Lived	Obst. & Gynec. latino-am. 4: 20-26, 1946.
233. Beacham, W. D., and Beacham, D. W.	1946	7½ months	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
234. Beacham, W. D., and Beacham, D. W.	1946	Full term	Well formed	3,543	Lived	Died	Obst. & Gynec. Survey 1: 777-806, 1946.
235. Beacham, W. D., and Beacham, D. W.	1946	Near term not deliv- ered	Dead, deformed jaw, clubfooted	2,976	Died	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
236. Beacham, W. D., and Beacham, D. W.	1946	Full term	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
237. Beacham, W. D., and Beacham, D. W.	1946	7 months	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
238. Beacham, W. D., and Beacham, D. W.	1946	Near term tubal	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
239. Beacham, W. D., and Beacham, D. W.	1946	10 months, tubal,	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
240. Beacham, W. D., and Beacham, D. W.	1946	8 months rupture	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
241. Beacham, W. D., and Beacham, D. W.	1946	Full term	Dead, macerated		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
242. Beacham, W. D., and Beacham, D. W.	1946	8 months	Living		Lived	Lived	Obst. & Gynec. Survey 1: 777-806, 1946.
243. Beacham, W. D., and Beacham, D. W.	1946	Full term	Dead		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
244. Beacham, W. D., and Beacham, D. W.	1946	7 months	Living, abnormal		Lived	Died	Obst. & Gynec. Survey 1: 777-806, 1946.
245. Beacham, W. D., and Beacham, D. W.	1946	Full term tubal rup- ture	Dead		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
246. Beacham, W. D., and Beacham, D. W.	1946	Full term	Calcified		Lived	Stillborn	Obst. & Gynec. Survey 1: 777-806, 1946.
247. Kushner, D. H., and Dobrzynski, F. A.	1946	8 months	Macerated, de- formed		Lived	Stillborn	Am. J. Obst. & Gynec. 52: 160- 161, 1946.
248. Lee, A. F.	1946	Full term	Living	2,778	Lived	Lived	Northwest Med. 45: 40-41, 1946.
249. Waters, H. S.	1946	Full term, tubal rup- ture, 4 months	Living	3,175	Lived	Lived	J. Obst. & Gynec. Brit. Emp. 53: 285-288, 1946.

baby weighing 10 pounds, 3 ounces lived; another that was four to five weeks overdue weighing 11 pounds, 1 ounce, also lived. Most of the babies that lived were delivered at term; none were under seven months.

Bland reported a maternal mortality rate of 34.7 per cent for 240 cases of late extrauterine pregnancy collected from the literature from 1813 to 1907, and a mortality rate of 16.7 per cent for sixty-one cases collected from 1907 to 1923.

Cornell and Lash reported a maternal mortality of 14.3 per cent in 236 collected cases of abdominal pregnancy (Table I).

All thirteen of our personally observed cases* occurred in Negro patients, although only about one-half of the obstetric patients in the Medical College of Virginia Hospitals are of this race. Early ectopic pregnancies in these hospitals occur in about the same percentage of white and Negro patients. The fact that late extrauterine cases occurred only among the Negro patients may indicate that these women sought medical care after their symptoms had persisted for a long period of time.

Most of our patients were between the ages of 25 and 35 years. Four were between 20 and 25 years, five between 26 and 30 years, three between 31 and 35 years, and one was 40 years old.

Previous operations could not be a factor in this series because not one of the patients had ever been subjected to a laparotomy.

TABLE II. THIRTEEN PERSONALLY OBSERVED CASES OF LATE EXTRAUTERINE PREGNANCY, DURATION OF PREGNANCY, CONDITION OF FETUS, MORTALITY

CASE	YEAR	AGE OF MOTHER	PREVIOUS PREGNANCIES	WEIGHT (GRAMS)	DURATION OF PREGNANCY CONDITION OF FETUS	RESULT	
						MOTHER	CHILD
1	1930	40	gravidia iii para i	2,230	40 weeks living and normal	died 7 days after oper- ation	lived
2	1932	25	gravidia iii para ii	2,680	42 weeks macerated	lived	stillborn
3	1932	34	gravidia i para 0	2,438	48 weeks macerated	lived	stillborn
4	1932	20	gravidia i para 0	2,069	36 weeks living and normal	lived	lived
5	1934	25	gravidia ii para i		15 months macerated	lived	stillborn
6	1935	36	gravidia iv para ii		28 weeks macerated	lived	stillborn
7	1935	23	gravidia ii para i	4,422	44 weeks macerated hydrocephalic	died 18 hours after oper- ation	stillborn
8	1936	32	gravidia iii para ii	3,487	42 weeks macerated	died 3 months after oper- ation of other con- ditions	stillborn
9	1937	30	gravidia iii para ii	1,474	24 months macerated, unrup- tured tubal pregnancy	lived	stillborn
10	1937	26	gravidia iii para 0	3,033	36 weeks living and normal	lived	lived
11	1944	32	gravidia iv para ii	2,891	40 weeks living and normal	lived	lived
12	1945	22	gravidia ii para 0	3,005	44 weeks not delivered	died before operation	stillborn
13	1946	30	gravidia ii para i	2,664	38 weeks living and normal	lived	lived

*For lack of space, the detailed case reports are not included.

Nine patients gave a history of one or more spontaneous deliveries prior to the extrauterine pregnancy and three of these reported, in addition, one or more spontaneous abortions. Two patients had abortions previously but no full-term pregnancies. Two patients had no earlier pregnancy, and one of these has since had a normal term intrauterine pregnancy.

The maternal mortality in late extrauterine pregnancy remains too high. Experience with our cases and a review of the literature convinces us that leaving the placenta with no attempt to separate it whenever its removal might cause hemorrhage or other difficulties reduces the mortality in patients with extrauterine pregnancy.

Operation for a late extrauterine pregnancy, as in any ectopic pregnancy, should be performed as rapidly as possible after the diagnosis is made, because of the high maternal mortality rate in cases of 28 weeks' or more duration. As shown in an earlier communication by the author, the maternal mortality rate in 115 cases of early ectopic pregnancy was 1.7 per cent, whereas in the thirteen cases of late extrauterine pregnancy, the maternal mortality rate was 30.76 per cent.

This opinion is in agreement with that of Bland and Montgomery (1939), who stated that recognition of ectopic gestation prior to rupture calls for immediate removal, for the welfare of the mother comes first, and operative methods should be instituted regardless of the stage of the pregnancy. A gestation of four or five months, they stated, calls for prompt removal, but there is less urgency in the eighth or ninth month, and the operation may be deferred two or three weeks in order to save the infant, unless there is a false labor with death of the child. Champion and Tessitore (1938) believe that if the infant is viable, operation with conservative handling of the placenta is indicated; if the fetus is dead, operation should be deferred six to eight weeks until the placental circulation has atrophied. DeLee suggested deferment from seven to twenty days for the same reason, but Beck believed, as McNeile (1937) points out, that in the interest of the child it may be desirable to postpone operation until after the thirty-eighth week. Tonneau disagreed, stating that there is risk of a secondary infection of the fetal sac, as shown in his case in which the fetus was within Douglas' pouch. He believed the infection was from the intestine.

In our own series of thirteen cases, seven fetuses were macerated, one of them having hydrocephalus. Winckel's statement in 1904 that half of the fetuses in ectopic pregnancy are deformed has been frequently challenged, but Bland in 1939 stated that healthy infants are rarely found, that usually they die within a few hours or days after delivery, and more than one-half are deformed. Mahfouz, however, in 1938 reported that in his series of 120 cases the fetuses which advanced to term, whether inside or outside the tube, showed little or no deformity, and the babies would certainly have been saved if the patients had been admitted in time. Some of the fetuses which died at an early age showed marked malformations, and about 3 per cent were calcified. One of his patients had carried the fetus for fifteen years and had four living babies in the meantime. Mundell in 1933 reported a deformity in eight of forty-nine live babies; in thirty-four dead babies there was deformity in one, and twenty-eight were macerated. In Champion and Tessitore's series, thirty-seven fetuses died (58 per cent), and one-half were macerated. In several instances the fetus was retained for many years, in Hardy's case for ten years, in Galabin's case for twenty-one years.

It is also evident that many more mothers and babies can be saved when late extrauterine pregnancy exists, if women advanced in pregnancy are examined more carefully. A correct diagnosis before the induction of labor or abdominal delivery is attempted enables the operator to anticipate unusual difficulties, and consequently reduces the risk to the patient.

Each new case of extrauterine pregnancy presents new problems in diagnosis and treatment. The management of the placenta in late extrauterine pregnancy is unquestionably an important factor in determining maternal mortality. Beck, 1919, advocated that the placenta be left in situ in abdominal pregnancy if its blood supply could not be easily ligated. He also advised closure of the abdominal wound without drainage in these cases. He had proved experimentally in animals that a normal placenta can be absorbed from the peritoneal cavity without harmful results to the animal. Since the publication of Beck's paper, it has become an accepted practice to leave the placenta whenever its removal can cause hemorrhage or other difficulties, and to close the abdomen without drainage. The use of this procedure has reduced the mortality associated with these cases. Case 4 in our series illustrates the excellent results, without development of further complications one may obtain with this treatment.

TABLE IV. MORTALITY FOLLOWING DIFFERENT MANagements OF PLACENTA

PROCEDURE	NO. CASES	NO. DEATHS	MORTALITY RATE
Placenta removed in toto	3	1	33.33
Placenta removed partially, marsupialization	3	0	0
Placenta left, marsupialization	1	1	100
Placenta left, abdomen closed	5	1	20

Two of the patients (Cases 8 and 12) in whom the placenta was left and the abdomen closed later developed drainage from the abdominal incision. One patient (Case 8) had an elevation of temperature after operation, but the abdominal incision healed by primary union. Later a sinus developed in the lower portion of her abdominal wound. She then went home against advice, attempted suicide at home by poisoning, and was later confined in a mental institution. She was re-admitted to St. Philip Hospital three months after delivery and died four days later. This death should not be charged to the extrauterine pregnancy, since the suicidal drugs she took may have been harmful and her mental condition prevented proper nutrition and management of her case.

Case 11 illustrates one of the dangers encountered when the placenta cannot be removed. This patient's placenta was attached to the rectum, the ileum, the uterus, and the broad ligament. The placenta was left and the abdomen closed. Her abdominal incision healed by primary union, but ten days after the operation drainage occurred from the lower portion of the incision; cultures from the exudate were positive for *B. coli*. Whenever the placenta is attached to the intestine, the danger of infection and suppuration is increased. This should not prevent one from leaving the placenta and closing the abdomen without drainage, but it necessitates a careful follow-up of the patient so that drainage can be established if necessary. A second operation on these patients for removal of the placenta has been suggested by some writers. We doubt the necessity for and the wisdom of such an operation except in very rare cases. Case 11 illustrates the results one may obtain with conservative treatment even if the placenta is not absorbed and there is drainage from the abdominal incision.

In two cases in which the babies were alive at the time of operation and the placenta was left in situ, positive Friedman tests were obtained on specimens of urine from the patients for thirty-five days after operation.

When an operation is performed for an abdominal pregnancy careful incision in the anterior abdominal wall should be made. The operator should avoid any attempt to separate the fetal sac and to remove the placenta until he is reasonably sure the blood vessels supplying the placenta and the sac can be

Less frequent, but equally suggestive, is a history of severe indigestion, constipation, and loss of weight. Frequently these symptoms are associated with anemia. In more than half of the cases the fetal movements were reported as either very high or very low. The latter symptom was associated most frequently with intraligamentous pregnancy.

The position of the fetus is usually high in abdominal pregnancy, and in most of these cases the baby is extended or at least poorly flexed. In Case 12 the fetus was unusually high in the abdomen, but otherwise its attitude seemed normal. It is possible for an abdominal pregnancy to have such a thick sac that the fetus may be flexed almost as much as it is in a normal uterus. On abdominal palpation the fetus is usually noted in close proximity to the anterior abdominal wall. In broad-ligament pregnancy the baby is usually below the level of the umbilicus, assumes an abnormal position, and frequently seems compressed and overflexed, as demonstrated by roentgen examination of four such patients in this series.

In late extrauterine pregnancy a vaginal examination usually reveals certain characteristic findings. The cervix is long, thick, and fairly firm. The cervical canal is usually closed, but about the thirty-sixth week it will sometimes admit one finger. We have not seen any case in which the cervix was soft as it is in an intrauterine pregnancy at term. If the pregnancy is intraligamentous, the cervix is usually in an abnormal position, frequently high, and pushed to one side. In abdominal pregnancy the cervix is in an abnormal position only when the placenta is attached in the pelvis or at the pelvic inlet. The position of the cervix varies as the position of the uterus changes. The size of the uterus usually increases to that of a three months' pregnancy. After death of the fetus the uterus slowly returns to normal size.

The dangers of unnecessary attempts to induce labor with pituitrin and too much manipulation, especially attempts to rupture the membranes and other mechanical methods of initiating labor, are illustrated in three cases (Cases 1, 7 and 12). Three of the four patients who died had received earlier treatment at home or in other hospitals in an effort to induce labor before the correct diagnosis was made. These patients were admitted to the St. Philip Hospital because the cervix had not dilated and they could not be delivered. Patient No. 1 had thought she was in labor for four days before entering the hospital, and it seems probable that the correct diagnosis was not made until the time of operation on this patient. In all other instances the correct diagnosis was made previous to operation. In one case (Case 7) the diagnosis was made and the patient operated upon the day of admission to the hospital. Before admission she had been severely ill for three weeks. Early attempts to induce labor medically and instrumentally had failed, and her condition was hopeless at the time of admission. Another case (Case 8) was not diagnosed at the time of admission, and an attempt to induce labor was made in the hospital before the extrauterine pregnancy was diagnosed. Following the diagnosis an operation was performed. In this case the attempt to induce labor did no harm, as the physician found the cervix too tight to permit introduction of a Voorhees' bag. One patient (No. 12) had received various treatments before she was referred to the hospital, but no accurate history of what had been done was obtainable. She was tentatively diagnosed on admission as having an extrauterine pregnancy, but developed a *B. Welchii* infection before the diagnosis was positive.

It seems probable that at least three of these patients (Cases 1, 7, 12) might have survived if they had entered the hospital earlier, and before they had been subjected to attempts to induce labor. The mortality rate for patients with late extrauterine pregnancy can be decidedly decreased if early diagnosis is made and meddlesome interference avoided.

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Discussion

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—Dr. Ware would appear to have had the good fortune of an uniquely extensive personal experience in the subject of his presentation. I have seen and operated on only three such cases in thirty-four years of direction of a large service, he four times that number in one-half that time.

The relatively large number of these cases coming to his clinic would appear to connote in the locality served by him either or both of the following conditions: first, that the clientele that they derive from do not seek medical advice early in abnormal pregnancy, or, second, that the type of medical service they do seek fails to recognize and properly treat those early abnormalities which lead to late extrauterine pregnancy. There is apparently much room indicated here for a double-barreled program of education designed to reach both laity and doctors.

Especially is this need for physician education exhibited in those cases improperly manipulated before admission to Dr. Ware's service. Any least appreciation of the conditions suitable for such manipulation would have demonstrated that they were *not* present in these cases, and the attendants would have been at once on their guard.

Dr. Ware's discussion of the symptoms and signs of late ectopic gestation is logical. Careful study of it may be helpful to each of us in relation to recognition of this relatively infrequent condition.

He is to be congratulated on the surgical ingenuity and resource with which he has met extremely varying conditions. He properly insists on the prime necessity for individualization of these cases.

His maternal results are good, in consideration of the handicap against him represented by mismanagement of some of the cases before coming to his hands. I believe his fetal results are unusually good in comparison with other experience.

His present larger series bears out his previous showing that where an entire ectopic mass cannot be definitely isolated, and its pedicle readily dealt with, best results attend leaving the placenta in situ, and closing the abdomen.

DR. LOUIS H. DOUGLASS, BALTIMORE, MD.—Recently in Baltimore we had occasion to look up all the abdominal pregnancies over a twenty-five-year period in all of the hospitals in Baltimore. There were twenty-six such cases, and, fortunately, we were able to get from the Health Department information about all of the viable births during that time. Our total was twenty-six cases in 425,620 live births, or an incidence of 1:16,370. It was sixteen times as high in the Negro race as in the white. I thought this might be interesting, in view of the paper this morning. Our total maternal mortality in this whole series was eight and, peculiarly enough, the rate was the same as Dr. Ware's, 30.77 per cent. In the first twenty years the maternal mortality was 41.7 per cent, whereas in the second twelve years, with the improvement in treatment and care, leaving the placenta in, it fell to 21.4 per cent. Our fetal mortality was 77 per cent.

I would like to stress one thing that Dr. Wade mentioned, and this is so self-evident that little is said about it; that is, that in many of the cases where the condition is suspected, we can rule out abdominal pregnancy by putting our hands on the mass. If Braxton Hicks' contractions are felt, the pregnancy is in the uterus.

easily ligated. The use of coagulants now available may enable one to control a moderate amount of oozing but this procedure may not overcome more extensive hemorrhage.

The use of penicillin and sulfa drugs may prevent or decrease infection in the placenta when it is attached to the intestine and left in situ and the abdomen is closed without drainage. The more frequent use of transfusions since the establishment of blood banks has decreased the maternal mortality rate associated with operation for abdominal pregnancy.

Summary and Conclusions

1. Observations on 13 cases of extrauterine pregnancy of twenty-eight weeks' or more duration have been presented, together with a review of 249 cases reported in the literature since 1933. The maternal mortality in the 12 operated upon was 25 per cent including that of a mother who left the hospital and died three months after operation. The maternal mortality for all 13 cases was 30.76 per cent including one woman who died undelivered.

2. A history of lower abdominal pain persisting since the onset of pregnancy or soon thereafter, accompanied by indigestion, constipation and sometimes irregular vaginal bleeding suggests an extrauterine pregnancy. The absence of uterine contractions when the fetus is palpated, a transverse or abnormal position of the fetus, a firm, long cervix, and a small empty uterus confirm the diagnosis. Roentgen examination of the abdomen and hysterosalpingograms were valuable aids in confirming the diagnosis.

3. An extrauterine fetus can remain viable and continue to grow after repeated episodes of uterine bleeding.

4. Regular rhythmical uterine contractions were observed in a patient with an extrauterine pregnancy.

5. The treatment for each case must be individualized. The placenta should be left in situ and the abdomen closed without drainage whenever removal of the placenta may cause hemorrhage or damage to a vital organ. Removal of the placenta should be reserved for those cases in which the placental blood supply can be easily tied off and the placenta is not attached to a vital organ.

6. The placenta can be absorbed from its attachment in the peritoneal cavity without causing elevation of temperature or adhesions in the pelvic cavity.

7. When the placenta is left in situ, positive Friedman tests have been obtained on urine from the patient thirty-five days after operation.

8. Transfusions of whole blood and the use of new coagulants may be life-saving measures in combatting hemorrhage at the time of operation.

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THE TREATMENT OF PELVIC ENDOMETRIOSIS

HERBERT E. SCHMITZ, M.D., AND JANET E. TOWNE, M.D., CHICAGO, ILL.

(From the Department of Gynecology and Obstetrics, Loyola University,
Mercy Hospital Clinics)

THE treatment of pelvic endometriosis is either radical or conservative. The complete destruction or removal of all ovarian tissue results in regression of the ectopic endometriomas, but, inasmuch as most women suffering with this condition are in the childbearing period, this is a costly price to pay. If conservatism could be practiced without serious secondary procedures being necessary in case of failure, then the radical treatment could be reserved for women at or near the menopause. In our clinic this has been the aim. We have now 130 cases treated with this intent: namely, to preserve ovarian function if possible and permit childbearing. Lesions of the uterus designated adenomyoma or adenomyosis have been excluded in this study because they occur in later years. Adenomyosis belongs definitely in the second half of the generative period, while endometriosis occurs in women at the height of their sex life. Dreyfus⁴ believes that the two conditions have a different origin because of the rarity of the combination of the two. The etiology of endometriosis is still unsolved but the hypotheses of Sampson,²² Meyer,¹⁵ Novak,¹⁷ and Halban⁸ are most widely accepted.

Material

Four methods of treatment have been employed in the handling of our cases. The group of 130 is, therefore, divided in Table I according to the treatment used in each case. A few cases were treated by as many as three methods before complete relief was obtained. It is for this reason that the tables showing type of treatment show more therapeutic procedures than we had cases.

TABLE I. PELVIC ENDOMETRIOSIS, 1941 TO 1946

Surgical group	57	43.9
Irradiation group	17	8.3
Hormone group	18	13.9
Untreated	25	19.3
Inconclusive	19	14.6
Total	130	100.0

The follow-up of this group is from one to four years in all but the 19 cases listed as inconclusive. These patients could not be traced and, therefore, are excluded. Periodic examinations are still being done on the remainder. Until they have all passed through the menopause, one cannot draw final conclusions. We feel, however, that enough data has accumulated to warrant this report.

Read at the Fifty-Eighth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

There was one rather interesting case in our group. The patient was in a hospital in Baltimore in 1931 with a diagnosis of cirrhosis of the liver and ascites. She was a chronic alcoholic. Large amounts of fluid were withdrawn and it promptly filled up again. She signed a release, went home, apparently recovered, and came in to see us in 1934, pregnant. She was delivered spontaneously at full term. The day she was to leave the hospital we had a flat plate of the abdomen made, which showed a mass of fetal bones in the pelvis, so that her "cirrhosis" of the liver in 1931 had been an abdominal pregnancy. She refused operation and said she would keep the fetal skeleton since she had had it so long. We finally found this patient in 1946. She was still living and an x-ray showed that she still had the fetal skeleton in the pelvis.

DR. WILBUR E. HOFFMAN, Charleston, W. Va.—The first case of abdominal pregnancy I saw was when I was resident at the University of Maryland Hospital. This was a Negro girl; and we could not hear a fetal heart beat. One man on the service said he heard it, however. Dr. Douglass and I operated on this patient. When the placenta was removed the patient bled to death on the table. Since then I have seen only three cases in my private practice. Of the three, we obtained two living babies. We left the placenta intact in these three cases and they all recovered.

One factor concerning the diagnosis of these cases will be found very true by watching—all I have seen have been after eight months' gestation. If an x-ray is taken on admission and another in a week or ten days, it will be found that the baby has not changed position at all. In intrauterine pregnancy a change in position of these babies may be found.

DR. WARE (Closing).—One of the patients operated upon because of an abdominal pregnancy was delivered of a normal living baby. The placenta was left in situ and the abdomen closed without drainage. This patient's temperature remained normal, but a mass which we thought was the placenta was palpable in the lower abdomen and pelvis for six months. Two years later she was delivered by cesarean section of a normal intrauterine pregnancy. Careful examination of her peritoneal cavity revealed only a small adhesion of the omentum to the middle third of the right Fallopian tube. No other adhesions were found.

patient had a colostomy at the first operation and, after microscopie confirmation that the lesion was benign, was castrated by means of x-rays. Resolution was satisfactory, but the patient expired at a later attempt to close the colostomy. It is our observation that patients with rectal invasion respond satisfactorily to castrating doses of x-ray, therefore surgical resection which is dangerous is not necessary. The eleven pregnancies, an incidence of 23.6 per cent, we feel, justifies the conservative treatment, as most of these patients gave sterility as one of their major complaints. Seven of the forty-seven patients were single, so the actual incidence of conception rises to 27.5 per cent.

TABLE IV. ENDOMETRIOSIS CASES TREATED BY IRRADIATION

	COMPLETE RELIEF	PARTIAL RELIEF	NO RELIEF	TOTAL	AVERAGE AGE
Permanent menolysis	17			17	36
Temporary menolysis	12			12	31.3
Secondary irradiation		1		1	34
Pregnancies	2			3	
	(3 babies)				

In this group of twenty-nine patients, seventeen were given a castration dose of x-ray, and all have remained free of symptoms. Their average age was 36 years. Twelve patients were given a temporary menolysis of from three to eight months' duration and, with the return of the menses, have remained free of their discomfort. This group averaged 31.3 years of age. There will undoubtedly be a high recurrence rate among these patients, but many will have advanced in age sufficiently so that x-ray castration can be used without too much discomfort to the patient. One patient, already mentioned in the discussion of surgical therapy, was treated with x-ray to cause a temporary menolysis after conservative surgery had failed to result in pregnancy. She conceived shortly after this therapy and delivered a normal infant. Four years later her symptoms were again so severe she was castrated with x-ray. The other patient who has delivered twice was referred by Dr. Harold Gainey of this Society, and he has reported on July 19, 1947, that she now has a normal pelvis.

Hormonal Therapy

Androgen therapy was used in fifteen cases of this study, the average age for this group being 29.3 years. None of these patients had previous surgery, so that the diagnosis is purely clinical after exclusion of all other conditions. We realize that there may be errors in this group, but agree with Gardner⁶ that a clinical diagnosis of endometriosis can be made with a good deal of accuracy. In the future we shall employ culdoscopy as practiced by TeLinde²¹ to obtain tissue for microscopic confirmation of the diagnosis. These patients were young with minimal pathology, small nodes or single small cysts, but with definite relationship to the menstrual cycle. It was our aim to carry these patients as long as possible before instituting more severe procedures. One patient conceived during this treatment and has delivered a normal infant.

TABLE V. ENDOMETRIOSIS CASES TREATED BY HORMONES

	COMPLETE RELIEF	PARTIAL RELIEF	NO RELIEF	TOTAL
Androgens	6	8	1	15
Estrogens	1		2	3
Secondary surgery		1	1	2
Secondary irradiation				
Pregnancies	1			1

Age

The average age of the 130 cases is 32.6 years, which is lower than the age given by Counseller,³ Haydan,⁹ Allen,² and others. Table II gives the average age for each of the groups in Table I.

TABLE II. AVERAGE AGE OF PATIENTS WITH ENDOMETRIOSIS

Surgical group	32.1
Irradiation group	36.5
Hormone group	29.3
Untreated group	33.6
Average age	32.6

The age of the patient definitely influences the choice of therapy. The older patient is best treated by radical means, as conservative treatment cannot be of sufficient benefit to risk the necessity of secondary therapy.

Surgical Group

Fifty-seven, or 43.9 per cent of the 130 patients were treated by surgical means. This is by far the most satisfactory form of treatment because it permits a careful inspection of the peritoneal cavity and microscopic confirmation of the diagnosis. Table III divides this group into those treated by radical surgery (removal of both ovaries with or without hysterectomy) and conservative surgery (preservation of ovarian tissue).

TABLE III. ENDOMETRIOSIS CASES TREATED BY SURGERY

	COMPLETE RELIEF	PARTIAL RELIEF	NO RELIEF	TOTAL	PER CENT
Radical surgery	10			10	17.6
Conservative surgery	25	12	10	47	82.4
Secondary surgery	0	1	3	4*	7.0
Secondary irradiation	0	11	7	18	31.5
Pregnancies	9	2		11	23.6
(11 babies)(1 after x-ray)					
(1 before x-ray)					

*One patient expired after closure of colostomy.

The group treated by removal of all ovarian tissue averaged 35.5 years. The disease was so widespread it was thought unwise to temporize. All recovered. Forty-seven patients were treated by conservative measures such as unilateral oöphorectomy, resection of an ovary or both, cautery or resection of implants, and uterine suspension to prevent recurrence of adhesions in the cul-de-sac. Only two patients had resection of the presacral ganglion, as this is more effective in adenomyosis than endometriosis. The average age of this group was 30.6 years. Twenty-five have been completely relieved and nine of the twenty-five conceived and bore eleven infants. One was a stillborn due to abruptio placentae. Twelve patients received temporary relief of from one to four years, one had further surgery, and eleven had to have subsequent x-ray therapy because of increasing discomfort. Two of the eleven became pregnant and gave birth to living infants. The one patient, four years after delivery, had to have a permanent castration by x-ray, but is very happy with her only child and feels that the conservative surgery was very worth while. The other patient had recurring symptoms after one year and was given a temporary x-ray menolysis after which she conceived and carried to term. The remaining ten cases treated by conservative surgical means had no relief and were then re-treated surgically in three instances and by x-ray in seven. Of those retreated by surgical means, three had bowel invasion with definite constriction. One

patient had a colostomy at the first operation and, after microscopic confirmation that the lesion was benign, was castrated by means of x-rays. Resolution was satisfactory, but the patient expired at a later attempt to close the colostomy. It is our observation that patients with rectal invasion respond satisfactorily to castrating doses of x-ray, therefore surgical resection which is dangerous is not necessary. The eleven pregnancies, an incidence of 23.6 per cent, we feel, justifies the conservative treatment, as most of these patients gave sterility as one of their major complaints. Seven of the forty-seven patients were single, so the actual incidence of conception rises to 27.5 per cent.

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Androgens	6	8	1	15
Estrogens	1		2	3
Secondary surgery		1	1	2
Secondary irradiation				
Pregnancies	1			1

Six of the group have complete relief of symptoms as long as they continue taking oral testosterone in daily dosage of 10 milligrams. The initial effect was obtained by intramuscular injections of varying dosage as not to cause masculinization of the patient. We have never resorted to the use of testosterone in diffuse endometriosis as advocated by Hirst¹¹ and Miller,¹⁶ as our preference here is for x-ray therapy. Eight patients have partial relief from this form of therapy and can "carry on" with the residual symptoms. One patient had no relief. Three patients have been treated with estrogens in an attempt to control symptoms by inhibiting ovulation. Two had no relief, but one has taken 5 milligrams of stilbestrol daily for two years and manages quite well. The two who were not benefited have refused surgical treatment which had been advised.

No Treatment Group

Twenty-five patients have received no therapy for various reasons. Six, who averaged 41.5 years of age, were permitted to enter the menopause. One of these was but 28 years old, an arrested case of pulmonary tuberculosis, who had a functional amenorrhea. Another, 36 years of age, had an early menopause. The remaining four were 44, 45, 47, and 49 years of age. Eight patients who averaged 30 years of age are being watched but not treated because of minimal discomfort and their ages. Eleven patients who averaged 34.8 years of age refused the treatment suggested. Two of the group under observation have conceived and are receiving prenatal care. In this group we again have to rely on clinical diagnosis. It is hoped that all patients can be followed until a final, positive diagnosis is obtained.

TABLE VI. ENDOMETRIOSIS CASES NOT TREATED

Spontaneous menopause	6	41.5 (Age)
Watchful expectancy	8	30.0 (Age)
Refused treatment	11	34.8 (Age)
Pregnancies	2	

Nineteen of the 130 patients have been lost or insufficient data were obtainable to confirm the diagnosis of endometriosis. Although the clinical diagnosis was relied upon in some of the cases included in this series, the evidence had to be convincing and more than one examiner's opinion was obtained.

Discussion

The incidence of pelvic endometriosis is in the neighborhood of 10 per cent (Meigs,¹⁴ Haydan,⁹ Allen,² and Fallas and Rosenblum,⁵ etc.) which in private material, according to Meigs, is 28 per cent and Holmes finds an incidence of 26 per cent. This incidence is higher than that of pelvic inflammatory disease in private cases. Our own average age of 32.6 years agrees with the findings of Counseller,³ Payne,¹⁹ and Meigs¹⁴ that the greatest frequency of endometriosis is in the middle third of reproductive life. The associated sterility demands conservative yet intelligent management. Our incidence of conservative therapy (82.4) is higher than in most series reported. Allen,² Haydan,⁹ Pemberton,²⁰ and others report conservatism in a lower percentage. Albrecht¹ treated six cases by producing temporary amenorrhea with x-rays when recurrence had taken place following removal of implants at the time of laparotomy. Retrogression was complete and menses recurred. Individualization is necessary in each instance as the age of the patient, her desire for offspring, and the extent and location of the disease influence the decision as to the ideal treatment

for that particular patient. Forty-six and seven-tenths per cent of our group treated by conservative surgery had secondary therapy. This, we believe, is justifiable because of the 27.5 per cent who conceived and delivered thirteen term infants.

Secondary irradiation proved quite satisfactory, especially when permanent menolysis was achieved. In every instance the dose table of Gauss⁷ was adhered to and pelvic measurements were made according to our previously described technique. Careless administration of x-ray will result in undesired results such as castration when temporary menolysis is desired.

Hormone therapy with androgens in young patients with minimal complaints not only corroborates the diagnosis when it subdues the symptoms, but it may enable the physician to carry his patient to an age when more radical treatment would not be so costly. That some patients have pelvic endometriosis without discomfort and that others recover spontaneously has been our observation as well as Gardner's.⁶

The one death in this series resulted from closure of a colostomy which had been performed for partial obstruction due to invasion of the gut by endometrial tissue. The response of this case and others in this series to x-ray or surgical castration causes us to agree with the observation of Heyman¹⁰ that resection or colostomy is unnecessary. As shown by Jenkinson and Brown,¹³ the regression following castration relieves the obstruction and further treatment is unnecessary.

Summary and Conclusion

Pelvic endometriosis occurs most frequently in the childbearing period and is a major cause of sterility. Conservative treatment, which will increase the possibility of conception is, therefore, the most desirable form of therapy.

A review of 130 cases treated with this intent shows that 57 or 43.9 per cent were treated by surgical procedure. Ten, or 17.6 per cent, required radical surgery (removal of both ovaries with or without the uterus). Forty-seven, or 82.4 per cent, had one or both ovaries preserved, and eleven later conceived giving birth to thirteen infants, an incidence of 23.6 per cent or a corrected incidence of 27.5 per cent.

X-ray therapy was employed in twenty-nine cases, of which seventeen were given sufficient dosage to cause a permanent menolysis. Twelve were treated with smaller dosage causing a menolysis of from three to eight months. In this group two conceived and delivered three infants, an incidence of conception of 16.6 per cent. X-ray therapy in this group proved satisfactory for secondary therapy when conservative surgery had failed.

X-ray therapy of sufficient intensity to destroy ovarian function is indicated in cases where endometrial tissue has invaded the bowel or bladder. It obviates the necessity of surgical resection with its increased risk.

Watchful expectancy or male hormone therapy is of value in cases with minimal disease and symptoms in young women. It enables one to postpone more radical procedures to the years when such therapy is less costly.

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25 EAST WASHINGTON STREET

Discussion

DR. CLYDE L. RANDALL, Buffalo, N. Y.—We have recently reviewed our choice of procedure when endometriosis was encountered at laparotomy during the years 1936 to 1945. This study revealed an incidence of endometriosis of only 4.7 per cent among women subjected to laparotomy on the Gynecology service of the Buffalo General Hospital during that ten-year period.

Evaluation of the therapy employed has been based on personal knowledge of the follow-up status of eighty-one patients among 142 cases of endometriosis operated on the Gynecology service of the Buffalo General Hospital during that ten-year period.

A few questions arise in regard to terminology. Dr. Schmitz speaks of the preservation of childbearing capacity as a desirable part of conservative therapy, but I would like to know what proportion of his forty-seven patients "operated conservatively" had a hysterectomy, and the number in which childbearing capacity as well as some ovarian tissue was preserved? I also regret that time did not permit him to report results in greater detail as far as age groups are concerned.

Classifying our treatment in accordance with the essayist's criteria, 86 per cent of 142 women operated upon for endometriosis, 94 per cent of those under 35 years, and 78 per cent of those 35 to 44 years of age, were treated conservatively (since some ovarian tissue was preserved in that proportion of each group). Moreover, childbearing capacity was preserved in 80 per cent of women under 35 years, in 48 per cent of women 35 to 44 years of age, and in only 7 per cent of women over 45 years of age.

Among the group in whom childbearing capacity is preserved, I am sure it is possible to anticipate a higher incidence of pregnancy than is generally realized. Considering women who were not only married but who actually wanted children, we found that 40 per cent had borne one or more after a conservative operation for endometriosis. Incidentally, we might well acknowledge here that the effect of pregnancy upon residual or recurrent endometriosis offers a problem that should justify a study of pooled data. Our observation of only nine cases over a short period of time so far suggests that disappearance of palpable lesions during pregnancy represents temporary and not a permanent regression of the disease.

I suspect Dr. Schmitz' group rarely remove the uterus when operating for this disease, for I would find it difficult to exclude from a review of external endometriosis "those patients with lesions of the uterus designated adenomyoma or adenomyosis." At least on our service, when 142 women were operated upon with adnexal endometriosis and the uterus was removed

in sixty-eight, or 47.8 per cent of cases, adenomyosis was reported within the wall of twenty-eight, or 41.2 per cent of those uteri.

Eighty-one operated patients have been followed two to twelve years. Twenty-eight per cent of those operated conservatively have to date been subjected to further treatment because of recurrent endometriosis. It is interesting that Dr. Schmitz thought it necessary to reoperate only four, or 8.5 per cent, of forty-seven patients, whereas he employed irradiation for recurrent disease in an additional eighteen, or 38.3 per cent, of the women originally treated by conservative surgery. I have no reportable experience with patients whose suspected endometriosis has been treated by irradiation alone. Eight of our patients have to date received postoperative irradiation, five for castration, and in three subcastration dosage was employed. We have to date resected endometriomas invading the bowel wall, but I feel the essayist has rightfully emphasized the effectiveness of irradiation under such circumstances.

I am glad to hear correction of a retroversion mentioned as part of a conservative operation for endometriosis. Throughout the ten-year period reviewed we have been convinced of the importance of freeing the uterus from the endo-sac and have practiced the method of ovarian bisection and resection recently emphasized by Beecham.

When our clinical diagnosis of endometriosis has not been verified by laparotomy we have to date not attempted to evaluate the course of this disease. While consideration of such cases would provide a desirable control group, until we employ the peritoneoscope or culdoscope to establish the diagnosis I feel we should give little consideration to unoperated cases.

Obviously, objections to unproved cases also arise when we attempt to evaluate hormone therapy. Occasionally, on a purely symptomatic basis, androgen therapy may be indicated for palliation, but I feel strongly that whenever endometriosis is suspected, its presence should be verified by adequate surgical exploration. Certainly exploration seems justified when we consider the evident effectiveness of conservative surgery in this disease. Androgen therapy may prove its chief usefulness among postoperative patients in whom symptoms or pelvic findings suggest recurrence to a degree that does not seem to warrant castration or reoperation. At least the temporary, symptomatic relief afforded by hormone therapy seems of value when we attempt to convince an apprehensive postoperative patient that she can live with her recurrent disease for a while.

In conclusion, I would like to suggest that "conservative" surgery for endometriosis should imply preservation of childbearing capacity as well as ovarian function, and that we should consider as "radical," treatment that results in castration at any time, or the loss of childbearing capacity under 35 years of age.

DR. CLAYTON T. BEECHAM, Philadelphia, Pa.—Some years ago Dr. Meigs wrote an editorial for *Surgery, Gynecology and Obstetrics* on the occurrence and progress of endometriosis in young women. He found it to be a common lesion in his private practice, as against the ward patients—the latter group bearing children while still young. Meigs felt that the prolonged period of birth control in those of a higher economic level contributed greatly to developing major endometriosis lesions by allowing uninterrupted menses for years. Therefore, if his theory is tenable, pregnancy is a valuable conservative therapeutic measure for endometriosis. In my experience I have found this to be true.

I think all of us should individualize in the light of pelvic findings and keep early endometriosis lesions in mind, whenever we advise contraception. It would seem that early childbearing is a prophylactic against widespread endometriosis in the younger groups.

We have seen many women who have postponed childbearing for any number of reasons, consult us because of severe endometriosis symptoms. In the majority of cases, pregnancy is advised. It is surprising the high percentage of patients who are able to conceive, in spite of marked endometriosis. As gestation progresses it is most satisfying to watch the palpable ectopic endometriosis fade away.

What happens after delivery? A small number will have a return of symptoms three to four months post partum, while others may go many months before they are aware of

their endometriosis. Careful guiding and encouragement of the patient will result usually in more pregnancies. The endometriosis may be subdued for years, or, if uncontrolled, surgery may be undertaken in a patient who has a family.

DR. WILLARD R. COOKE, Galveston, Texas.—Dr. Schmitz made no mention of a procedure which I have found most valuable in the treatment of pelvic endometriosis—so valuable, in fact, that since 1932 I have not performed radical extirpation in any case. This procedure is presacral sympathectomy and, where indicated, ovarian neurotomy. While I have at present no idea of the total number of cases in which these procedures were carried out, I have a complete follow-up on seven cases of massive endometriosis. These cases were all of the type in which the pelvic viscera were indistinguishably merged, upon vaginal examination, into a mass filling the pelvic cavity. Not only was the symptom of pain relieved, but there has been a complete or almost complete disappearance of the mass in every case, and two of the patients have since borne three children.

I feel that the semidisrepute into which these operations have fallen is due to two misconceptions, one anatomic, the other technical. It is useless to expect relief of pain in areas which lie outside the sensory distribution of the presacral plexus. This is particularly true of the ovaries, whose sensory nerve supply is entirely different and must be interrupted if relief of ovarian pain is to be secured. For instance, in one of the cases referred to above it was necessary to warn the patient that the pain due to an area of endometriosis overlying the right ureter above the pelvic brim would not be relieved. The second misconception is in regard to the technique of adequate excision of the presacral plexus. It is commonly stated that only the tissues anterior to the plane of the middle sacral vessels need be removed. This is far from true, since many of the fibers of the plexus pass posteriorly as well as anteriorly to the femoral vessels and the plexus itself is very widely distributed throughout the tissues anterior to the spine. We have found it possible to interrupt all of the essential fibers only by using the mesial surface of the femoral veins as a guide to the removal of the entire bloc of tissue between these vessels all the way down to the periosteum and ligaments of the under lying spine and/or sacrum for a vertical distance of at least three centimeters.

DR. G. D. ROYSTON, St. Louis, Mo.—There are two points I should like to mention. The first is the findings of inflammation without infection are suggestive of endometriosis. The second is the difficulty of making a differential diagnosis by means of the x-ray of malignancy from endometriosis involving the lower bowel wall.

DR. SCHMITZ (Closing).—I am sorry that offhand I cannot tell Dr. Randall the percentage of these patients who had hysterectomy. None of the conservative group did have hysterectomy. As I defined conservatism, I said preservation of the uterus and some ovarian tissue.

This question of birth control is of great importance as far as endometriosis is concerned. It is brought out again that these patients are in the middle third of their reproductive life with the complaint of sterility. Had they conceived early in their reproductive life they may not have suffered from endometriosis.

In answer to Dr. Cooke, I have included presacral sympathectomy. I said that it is of value in adenomyosis, but not in pelvic endometriosis.

In using androgen the dosage varies. We use sufficient dosage to control the symptoms, then try to find a clinical dose that will control the condition.

FIFTY-FOUR DEATHS OCCURRING IN PREGNANT PATIENTS WHO HAD HYPERTENSION*

ROBERT A. ROSS, M.D., S. S. LAMBETH, M.D., W. L. THOMAS, M.D.,
AND F. B. CARTER, M.D., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, Duke University Medical School)

THE material for this presentation was obtained from an analysis of the Duke Hospital charts and records of fifty-four patients who had blood pressure elevated above 140/90, and who died during pregnancy or in the immediate puerperium. The only selection of patients was the exclusion of thirty-five deaths of eclamptic patients. These were recently reported elsewhere.

We began this analysis by asking some of the questions about hypertensive pregnant women which we would like to have answered. We wanted to know more of their history and prenatal care, more of the important physical findings and associated complicating conditions. We wanted to find out what, if any, laboratory data are significant. We were interested in the labor and delivery of these patients, and finally in their mode of death.

We have approached the problem from the standpoint of patients who died due to failures of management. The fault may have been the patient's, the physician's, or the result of circumstances beyond the control of either.

The purposes of this study were twofold: first, to select facts from the records which will assist us to better estimate the prognosis of similar patients in the future. Second, to analyze our method of management for information which can guide our future therapeutic approach to such patients.

The problem of hypertension and pregnancy has received considerable attention in the past seven years. There is a large variation in the attitude of the authors^{1, 2, 3, 4, 7, 13, 16} whom we have consulted. We believe our analysis is justified by the statement in 1942, of Hamilton and Thompson,⁷ that further study is needed in order to establish any definite rules for the management of the pregnant woman with hypertension.

Table I presents the distribution of deaths by years. The steady increase in the relative importance of the hypertensive pregnant patient as a cause for maternal mortality is in keeping with the increase in chronic vascular renal disease as a cause of death in the general population.

TABLE I. YEARLY DISTRIBUTION

YEARS	DELIVERIES	TOTAL MATERNAL DEATHS	DEATHS WITH HYPERTENSION	PER CENT OF TOTAL DEATHS
1931-1936	1,564	85	17	20
1937-1941	3,302	72	20	28
1942-1946	6,101	49	17	35
Total	10,967	206	54	

*Presented at the Fifty-Eighth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

Table II shows the frequency with which previous hypertension could be diagnosed from the records of our group of patients. Since most were seen first in the last trimester of pregnancy, it was impossible to answer this question very accurately. We believe that most, if not all, of the fifty-four patients had previous hypertension at some time. We do not think it is absolutely necessary to differentiate hypertensive disease and late pre-eclamptic toxemia of pregnancy. In fact, we believe it may be impossible to do so late in pregnancy.

TABLE II. PREVIOUS HYPERTENSION

TOTAL PATIENTS	PREVIOUS HYPERTENSION NOT ASSOCIATED WITH PREGNANCY	HYPERTENSION WITH PREVIOUS PREGNANCY	INADEQUATE HISTORY
54	19	21	25

The age distribution of the fifty-four patients is given in Table III. Most of them were 30 years of age or over, which would be expected of patients with hypertensive disease.

TABLE III. AGE DISTRIBUTION

15-20	21-25	26-30	31-35	36-40	41-45	46-50	TOTAL
1	3	10	15	14	9	2	54

Forty-five of the fifty-four were multiparas. There were 29 Negroes and 25 white women in our group. Our delivery ratio of white to Negro is about eight to five. Except for two patients treated when the hospital first opened, all of this group were public ward patients. An estimate of their prenatal care is given in Table IV.

TABLE IV. ESTIMATE OF PRENATAL CARE

NO CARE HERE	ADEQUATE CARE OUTSIDE	PRENATAL CARE HERE
48	2	7

The average number of previous pregnancies for the group was 5.8; the average number of living children was 4.6 (Table V). The fate of the infant is a most important consideration in any pregnancy, and particularly so in pregnancies involving such sacrifices as those we are studying. Only seventeen of the fifty-eight infants survived the neonatal period, which is not a fair ratio for the investment of fifty-four (maternal) lives.

TABLE V. YEARLY DISTRIBUTION OF STILLBIRTHS AND NEONATAL DEATHS

YEARS	TOTAL	INFANTS OF PTS. WITH HYPERTENSION	% OF TOTAL
1931-1936	205	13	6
1937-1941	336	16	5
1942-1946	386	12	3
Total	927	41	

In our group, postmortem section was done four times without obtaining a living baby. We do not consider this a very worth-while procedure.

Browne and Dodds,¹⁵ in reporting 222 pregnant women with chronic hypertension, noted that when the diastolic pressure was 100 or more there was only

a 31.5 per cent chance for a living infant. In our group, fifteen of the sixteen patients whose infants survived had diastolic pressure greater than 100. Six pressures were 120 or greater.

TABLE VI. WEIGHTS (Gm.) OF LIVING CHILDREN

1400-1500	1600-1900	2000-2500	2600-3000	3100-3500	3600-4000	TOTAL
1	0	4	7	4	1	17

The average admission diastolic blood pressures for the group are presented in Table VII. The elevated blood pressure was the one common denominator of all the patients. Other points varied a great deal and made it impossible to classify all of them as to the exact pathologic process. We want to reiterate here that we are discussing hypertensive pregnant women. We cannot be sure how much pre-eclampsia, nephritis, or essential hypertension they had. In our study, we have learned that no single factor is of too much practical importance, because management should depend on the seriousness of the whole clinical picture.

TABLE VII. AVERAGE ADMISSION DIASTOLIC BLOOD PRESSURE

90-99	100-110	111-120	121-130	131-140	141 OR ABOVE
6	15	10	7	5	11

We have not recorded systolic pressures because their variability makes them of less value than the diastolic readings. It is felt by some authors⁵ that the pathologic process continues although the blood pressure has been greatly reduced. Goldring and Chasis⁵ have emphasized the futility of treatments directed only toward bringing down the blood pressure level.

In Table VIII an analysis of the changes found in the optic fundi is presented. These changes consisted of thinning of the vessels, increased light reflex, tortuosity of the vessels, A-V nicking, and in a few instances hemorrhages and exudates. Different opinions have recently been expressed about the value of the optic fundi as an estimate of prognosis in hypertensive cardiovascular renal disease. Hallum⁶ has emphasized their importance to the obstetrician. Goldring and Chasis⁵ have called attention to the frequent discrepancy between the height of the diastolic pressure and the extent of the arteriolar disease, as manifested in the retinas. They state that the fundi of patients with malignant nephrosclerosis may show few abnormalities, while extreme ocular changes are sometimes noted in patients who actually have benign hypertension. In our experience, the ocular changes were a relatively constant finding in these patients with a lethal exodus.

TABLE VIII. CHANGES IN OPTIC FUNDI

DEFINITE	NO CHANGES	NOT WELL VISUALIZED
38	5	11

Hamilton and Thompson⁷ have suggested that a grossly enlarged heart adds greatly to the risk of pregnancy for hypertensive individuals. Hearts weighing 400 Gm. or more were found at autopsy in fourteen of the group. The estimation of heart size in the other patients were made clinically and by x-ray. A total of twenty-five patients were thought to have enlarged hearts.

It is common knowledge that obesity adds to the hazards of hypertensive disease. In our series, thirty-three of forty-six patients were definitely over-

weight. The state of nourishment of eight patients was not recorded. These figures are certainly suggestive of an association between the two conditions in the pregnant woman.

The laboratory findings in hypertensive disease are seldom significant in the earlier stages. Whenever there are urinary changes, the prognosis is more serious. This was confirmed in our series of patients. Of fifty-one urine examinations, only seven were negative. In four of these, the hypertension was entirely secondary. The urine changes always included albuminuria, frequently cylindruria, and almost never hematuria.

Some blood chemistry findings are listed in Table IX. It is interesting that two total protein values were low (below six) with a normal A/G ratio, and five A/G ratio values were below one, whereas the corresponding total proteins were normal (six or above). The frequent alterations in plasma proteins may be due to the fact that our patients were malnourished. In this connection, twenty of fifty-three patients examined had lowered hemoglobin values (below 70 per cent). In only six of these patients was the low value associated with excess blood loss.

TABLE IX. BLOOD CHEMISTRY FINDINGS

	URIC ACID	PLASMA PROTEINS	A/G RATIO
Total obtained	43	22	21
Normal	8	7	4
High (4.0 mg. or more)	35	—	—
Below 6 Gm.	—	15	—
Below 1	—	—	17

The great frequency of elevated uric acid values among our patients is possibly significant. Chesley and his associates² have recently stated that the development of toxemia of pregnancy in patients who are already hypertensive is the really serious complication and hazard to their lives. The almost constant occurrence of urine changes and high blood uric acid values strongly suggests that most of our patients were suffering from hypertensive cardiovascular renal disease and superimposed pre-eclamptic toxemia.

An electrocardiogram was obtained on fourteen patients. In nine of these some sort of abnormality was reported. However, only in two patients was a definite diagnosis, auricular flutter, made. The other changes included left axis deviation and T-wave alterations.

The proper management of the pregnant patient with hypertension requires a great deal of judgment. It is difficult to decide when, and if, the pregnancy should be interrupted. In our study we have found that no set rules of management were followed. The decisions were individualized. Our observations on these patients merely show what happened to them. We can possibly draw conclusions from some of these occurrences.

Table X records the hospital days before delivery and death. The high number who died before the fourth day may indicate the seriousness of their condition on admission. The fact that one-half the group delivered in three days indicates early intervention, but the fact that nine patients died undelivered suggests a conservative attitude.

TABLE X. DAYS BEFORE DELIVERY AND DEATH

HOSPITAL DAYS BEFORE DELIVERY				NOT DELIVERED	HOSPITAL DAYS BEFORE DEATH				
0-3	4-6	7-10	11 or more	9	0-3	4-6	7-10	11-14	15 or more
27	11	5	2		19	11	10	6	8

An analysis of the labor and delivery of the fifty-four patients is presented in Table XI. Seven deaths following therapeutic abortion seems a high one when we recall that these were the results of efforts to relieve the patient of an early pregnancy. This treatment may be considered worse than the disease.

TABLE XI. GROSS ANALYSIS OF LABOR AND DELIVERY

THERAPEUTIC ABORTIONS	SPONTANEOUS LABOR	INDUCED LABOR	NOT DELIVERED	SPONT. VAG. DELIVERY	OPERATIVE VAG. DEL.	ABDOMINAL DELIVERY
7	22	16	9	19 (outside)	13 (outside)	6

Table XII gives supplementary information about the therapeutic abortions which is necessary to fully appreciate the statistics of Table XI.

TABLE XII. TYPES OF THERAPEUTIC ABORTIONS (FETUS LESS THAN 1000 Gm.)

1	Aborted outside (D and C for bleeding)
1	D and C (two-month size uterus). Uterus ruptured. Supravaginal hysterectomy
1	Artificial rupture of membranes at five and one-half months
1	Vaginal hysterotomy (700 Gm. fetus)
2	Abdominal hysterotomy and tubal resection (3 to 4 months)
1	Supravaginal hysterectomy (3 to 4 months pregnant)
7	

Table XIII presented an analysis of the cesarean section done on this group of patients. Three of these patients died of causes directly related to the hypertensive cardiovascular renal disease.

TABLE XIII. SECTIONS AND CAUSE OF DEATH

TYPE OF SECTION	SHOCK DUE TO RUPTURE OF UTERUS	SHOCK WITHOUT EXCESS BLOOD LOSS	CONGES- TIVE HEART FAILURE	UREMIA	EMPHYEMA AND CHRONIC NEPHRITIS	DEHIS- CENCE AND PERI- TONITIS
Classical without labor (4)	-	1	-	1	1	1
Classical with 4 hr. labor (1)	-	-	1	-	-	-
Porro (Rupture of uterus after 7 hr. labor)	1	-	-	-	-	-

The results of induced labor are compared with spontaneous labor (Table XIV).

TABLE XIV. COMPARISON OF LABOR WITH DELIVERY

TYPE OF LABOR	OPERATIVE VAGINAL DELIVERY	SPONTANEOUS VAGINAL DELIVERY	ABDOMINAL DELIVERY	DIED UNDELIVERED
Medically induced (4)		4		
Surgically induced (12)	6	4		2
Spontaneous (22)	7	12	2	1

One of the most interesting parts of this study was the effort to catalogue the patients as to the immediate mode of cause of death.

Table XV presents an analysis of these figures which is self-explanatory. Some of these patients received more attention than others. We have presented the autopsy and medical consultation figures because they afford some idea of the

TABLE XV. ANALYSIS OF CAUSE OF DEATH

	CON- GESTIVE HEART FAILURE	UREMIA	CEREBRO- VASCULAR ACCIDENT	SHOCK WITHOUT EXCESS BLOOD LOSS	AR- RHYTH- MIA	HYPERTENSION CON- SIDERED SECOND- ARY	TOTAL
Number in each group	14	8	3	12	1	16	54
Grossly enlarged hearts	10	4	2	6	1	2	25
Medical consultation	13	4	3	5	1	6	32
Autopsies	10	4	0	6	1	9	30

sort of study given them. The relative frequency of definitely enlarged hearts corresponds well with the severity of the vascular disease.

Tables XVI and XVII are presented figures to support the initial classification of the cause of death. It is fitting to remark here that the classification of death causes is a personal one. We readily admit that variations in the categories would almost certainly result if any other observers attempted to classify them. However, we think our classification affords an opportunity to study more adequately the course of hypertensive cardiovascular renal disease in the pregnant patient. Probably the most unexpected finding was the large number of patients who died in circulatory collapse. The blood pressure changes were always accompanied by cold moist skin and rapid thready pulse. The pressures fell very quickly from diastolic levels between 120 and 170 to an average of 50 to 60. No patient was included in this group in which the blood loss was excessive.

TABLE XVI. ANALYSIS OF THE UREMIA GROUP

	800	1000	1900	700	170	1500	165	1000
Output (c.c.)	↓ 200	↓ 450	↓ 740	±	↓ 40	↓ 150	↓ 0	↓ 0
Nonprotein nitrogen (mg.)	53 ↓ 84	33 ↓ 211	54 ↓ 72	61 ↓ 105	64 ↓ 165	48 ↓ 83	28 ↓ 54	35 ↓ 105

TABLE XVII. SIGNIFICANT DIAGNOSES HYPERTENSION SECONDARY GROUP

3	Pulmonary embolus
4	Puerperal endometritis
3	Rupture of uterus
1	Empyema
3	Placenta previa and premature separation (severe blood loss)
1	Indefinite
1	Anesthetic death (large goiter)
16	

As a result of this finding, an effort was made to locate references in the literature that hypertensive patients are more subject to, and tolerate less well, peripheral circulatory collapse. Moon⁸ refers to shock in toxemia of pregnancy. Adair and his associates reported an increased incidence of shock in toxemia patients. A careful study of their patients suggests that many had pre-existing hypertensive disease, complicated by toxemia. In fifteen of their sixteen severe patients, the optic fundi showed definite evidence of chronic vascular disease. The appearance of shock in pregnant nephritides and eclamptic patients has been noted by others.^{10, 11, 14}

No conclusive reference to shock in hypertensive patients was found in the literature. There is nothing to indicate that the operative procedures incident to labor and delivery are accompanied by more circulatory collapse in hyperten-

sive than in the normal patients. On the other hand, Lash¹² has recently stated, "We have already learned that hypertension without serious cardiac complication does not add much to the hazards of operation."

We have previously remarked in this analysis that most of our patients had evidence of pre-eclampsic toxemia as well as hypertensive disease. It may be that the frequency of shock in our group depends partly on the combination of conditions.

In Table XVIII, we have analyzed the labors and deliveries of our patients according to their mode of death. We have been looking for elements of operative trauma and have found more interference in the hypertension secondary group than in the others. This may indicate that in the "shock group" the circulatory collapse may have some other basis than "interference." Eight of the forty-five patients who were delivered had labor lasting longer than twenty hours and four longer than thirty hours. Eight patients had ether, one caudal, one spinal, ten local, and the remainder had no anesthesia.

TABLE XVIII. COMPARISON OF LABOR AND DELIVERY WITH MODE OF DEATH

MODE OF DEATH	SPONTANEOUS LABOR	INDUCED LABOR	UNDELIVERED	SPONT. VAG. DELIVERY	LOW FORCEPS DELIVERY	OTHER OPERATIVE VAG. DELIVERY	ABDOMINAL DELIVERY	THERAPEUTIC ABORTIONS
Congestive failure (14)	8	1	5	4	4		1	
Shock without excess blood loss (12)	6	3		4		4	1	3
Uremia (8)	4	3	1	6			1	
Cerebrovascular accident		2		2				1
Hypertension secondary (16)	3	7	3	2		5	3	3
Arrhythmia (1)	1			1				
Totals	22	16	9	19	4	9	6	7

Summary and Conclusions

1. The increasing problem of hypertension reflects itself in the pregnant female, especially in the colored patient.
2. The difficulty of accurately classifying toxemias of pregnancy even after autopsy is evident.
3. The ratio of living infants to dead mothers is recorded.
4. The elevated diastolic blood pressure was the common denominator of all fifty-four patients.
5. We believe that help from all consultant's sources is important and the simpler laboratory tests are worth while.
6. The hypertensive woman with enlarged heart, changes in the optic fundi, and albuminuria has a poor prognosis when pregnant. Serious consideration of interruption by the most conservative means should be given such patients, regardless of the stage of pregnancy, and contraceptive measures should be suggested.

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Discussion

DR. J. BAY JACOBS, Washington, D. C.—The worth-while purpose of this study has been stated, namely, to better estimate prognosis and to arrive at an effective form of treatment. However, the clinical material is of such type as to make it difficult to obtain proper evaluations. The majority of these patients had had little or no prenatal care; the incidence of occurrence in Negro and white is almost two to 1; and all of the patients died after very short hospitalization. It is evident that there was very little opportunity on the part of the clinicians to treat the condition much before death. For such reasons, I would state that probably none of these patients died due to failures of management.

We are told that eclampsia has been eliminated from this study, and at the same time the essayist emphasizes that he cannot be sure of how much toxemia, nephritis, or essential hypertension existed. Such hypertensive patients are probably very prone to the development of toxemia of pregnancy, and so perhaps the inclusion of eclampsia in such a study might be desirable.

I think we all agree with the essayist in emphasizing the importance of high diastolic pressure as one means for selecting these cases. I note also that he has a tendency to ignore high systolic pressure. Since most practitioners have learned to detect toxemia early because of elevated systolic pressure, resulting of course in lowered mortality due to toxemia, I would hesitate very much to publish this view because of the possible ill-effect upon men who are not experienced enough to evaluate published matter and who would be inclined to follow such views, especially since they emanate from a well-recognized clinic.

Since the desire to obtain a living infant is of paramount importance in any obstetric case, it is well to note that fifteen of the sixteen patients whose infants survived had diastolic pressures greater than 100 in this series, as compared to Browne and Dodds who reported only a 31.5 per cent chance for living infant in a series of 222 pregnant women with chronic hypertension. Perhaps this difference is due to the fact that the essayist advocates individual treatment for such cases, with what appears to be a tendency toward conservatism.

I would like to state a few facts and practical suggestions made by Dieckmann in the *Surgical Clinics of North America* (February, 1943). It should be remembered, however, that he is referring to hypertensive toxemia of pregnancy and not to an analysis of such deaths. He states that 5 per cent of all pregnant women delivered in hospitals in the United States have some evidence of toxemia, and that one-half of them have permanent vascular disease as a basis for the condition. He offers certain advice for the treatment of such patients both for their benefit and that of the infant, presuming of course that the patient is of high enough mentality to seek medical advice earlier in pregnancy.

Since such patients are known to have small babies, he has advocated the administration of 500 c.c. of 20 per cent glucose intravenously three times a day for a week at a

time as well as encouraging the patient to eat hard candy throughout pregnancy in order to help increase the size of the fetus. Since fetal death in these cases is frequently caused by abruptio placentae, retroplacental hematoma, or placental infarction, and since they all have the same etiology and are said to be amenable to treatment with vitamin E, such therapy may be worth trying, throughout pregnancy or at least after the twenty-fourth week.

Most of these women are fat and remain so in spite of thyroid medication, and for that reason their intake is kept at 2,000 calories, limiting fat intake and allowing 80 to 100 Gm. of proteins daily as well as a quart of skimmed milk. The importance of ample bed rest throughout pregnancy is emphasized.

Dieckmann states that his results indicate that the careful medical management of the toxemic patient, if begun early enough, will usually prevent further increase in the severity of the symptoms and signs until the cervix is "ripe."

The idea of individualized treatment as advocated by the essayist appeals to me. Considering the poor type of clinical material and the late stage in the disease when first seen and the large proportion of babies that survived, I would consider the results as favorable as might be expected.

DR. EMMETT D. COLVIN, Atlanta, Ga.—We encounter a large number of such patients in the obstetric clinics of Emory University, especially in those for Negro women. It is perfectly obvious that Dr. Ross' clinic must receive many of these women in a critical condition from sources outside of the University's prenatal clinic.

Several years ago in Dr. J. R. McCord's clinic, I surveyed the maternal mortalities occurring over a ten-year period. Sixty per cent of the deaths were among hypertensive women, mainly among multiparas whose pregnancy was complicated by chronic vascular disease alone or with superimposed toxemia of pregnancy. Many of the mortalities occurred among women whose histories revealed that near fatalities had occurred during previous pregnancies or labors. Some had refused surgical sterilization.

I desire to confine my remarks to a discussion of chronic vascular disease hypertension. In the management of patients with late pregnancy hypertension, we feel it important to differentiate between that of true toxemia and that of vascular disease. Especially is this important in the early stage of developing hypertension.

We have learned to attach great significance to the results obtained by study of the retinal vessels early in pregnancy, as well as late after hypertension has developed. Over 60 per cent of women with normal blood pressure readings and normal urinary findings, but showing a disturbance in the arteriovenous ratio and increased light reflex of the retinal arterioles early in pregnancy will develop hypertension four to six weeks from term. Bartholomew found this information obtained early in pregnancy, combined with blood pressure behavior, degree of albuminuria and symptoms, to be of great value in the diagnosis and management of developing hypertension late in pregnancy. The information is of special value in the final classification of the type of hypertension.

In addition, we have found that a careful study of the properly formalin-fixed placenta of a hypertensive patient offers valuable information in the final classification of the hypertensive woman. The conspicuous absence of subacute or acute infarction in the placenta of cases of chronic vascular disease and the presence of this type of infarction in those from true toxemia cases, we feel, has served well in the final classification of the type of hypertension which complicated the pregnancy.

If one reviews the charts of previous pregnancies of mortalities due to hypertensive complications, it will be found that the severity of the hypertension has increased as parity has increased and in many instances the woman was a near fatality in one or more of the previous pregnancies.

To me, the practical solution to the problem of hypertension due to vascular disease late in pregnancy lies not primarily in the manner of treatment, but in the accurate classification of the type of hypertension and prevention of future pregnancies in this group of women. So many of these women already have too many children at home.

BLOOD PLATELET STUDIES DURING PREGNANCY AND THE PUERPERIUM*

C. V. WARD, M.D., AND J. L. MACARTHUR, M.D., MONTREAL, QUEBEC

(From the Department of Obstetrics and Gynecology, the Montreal General Hospital)

A GREAT amount of work has been done on the estimation of blood platelets and the divergent findings are largely the result of differences in the methods of examination.

The blood platelet is so small, and its existence outside the body is so difficult to estimate that it is not surprising that many methods used to examine them yield many errors.

The enumeration of platelets as carried out on cutaneous blood is stated to have only a limited value, however, to discard all the evidence accumulated by employing this method would be discarding approximately three-fourths of the available knowledge on the variations in the number of platelets.

The mode of origin of the platelet from the megakaryocyte suggests that it is the product of the cell rather than a cell itself.

In the performance of their function, platelets unlike most cells are nearly always irreversibly altered or destroyed. These are essential points to keep in mind when studying the differences in platelet content between arterial, venous, and cutaneous blood.

The Origin of Blood Platelets

The origin of blood platelets is the source of much controversy. Tocantins¹ outlines numerous theories as to their origin, but tends to support the work of Wright² who states "blood platelets are detached portions or fragments of the cytoplasm of the megakaryocytes which are in such relationship to the blood channels in the bone marrow that detached portions of their cytoplasm are quickly carried by the blood current into the circulation."

Platelet production may occur whenever mature megakaryocytes exist, namely bone marrow, spleen, liver, and lungs. Many authors have stated that the spleen is one of the main sources of blood platelets. Splenectomy, however, is usually accompanied by a rapid rise in the number of platelets in the circulating blood. There is usually a concurrent increase in activity in the megakaryocytes of the bone marrow following splenectomy, strongly suggesting that the bone marrow is the main source of platelets.

Common Factors Which Influence the Number of Platelets in the Circulating Blood

Physiological.—There are significant differences in platelet counts carried out on arterial, venous, and cutaneous blood. In a series of forty males

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examined in Philadelphia by Tocantins,³ during the winter and spring, the average number of platelets found in blood taken from the arm was: arterial blood 350,000 venous blood 310,000, and cutaneous blood 250,000.

Posture.—Change of posture is stated to cause considerable variation in the number of platelets. Within fifteen seconds of suddenly getting up, after resting horizontally for one-half hour, the platelet count is decreased 20 per cent or more. On the other hand certain authors maintain that strenuous exercise causes a rise in the number of platelets while other authorities state that exercise or posture cause no alteration in platelet counts.

Season.—In man, according to Kemp,⁴ the number of platelets decrease during the summer months, while in the winter platelet counts from arterial and venous blood show a significant increase, counts carried out on cutaneous blood show no definite differences in the two seasons.⁵

Feeding.—The effect of feeding on the number of platelets is extremely controversial; many authors state that there is no change after ingestion of food, Benhamou and Nouchy⁶ state that an increase in the number of platelets after feeding is a constant factor in blood obtained from cutaneous puncture in man. The increase appears twenty minutes after the ingestion of food, and reaches its maximum in forty to sixty minutes with a return to normal within two hours.

Menstruation.—Pohle⁷ states that the average platelet count is at its lowest level on the day of onset of menstruation, rapidly rising to a level of 275,000, remaining constant for two weeks, then there is a steady slow progressive fall during the remainder of the cycle.

Drugs.—Arsphenamines produce a short transitory decrease in the number of platelets (McCarthy and Wilson⁸).

Ephedrine subcutaneously causes an increase in the number of platelets within five minutes in normal patients or patients with a chronic thrombopenia.

Ether anesthesia does not alter the number of platelets. Small or normal doses of such drugs as heroin, morphine, demerol do not significantly alter the platelet counts.

Pregnancy.—There is no general agreement as to the changes in the numbers of platelets during pregnancy. Rebaudi⁹ found a great increase in the first four months of pregnancy and also in the last month just before delivery. Benhamou and Nouchy¹⁰ observed only a slight increase in the last months of pregnancy. Bland, First, and Goldstein¹¹ found no important differences between platelet counts in the pregnant and the nonpregnant woman. A definite decrease appears to be fairly constant in the first stage of labor with a return to normal level in the second stage.

One author states that in moderately toxic patients the number of platelets does not differ from that of normal pregnant patients. In severe pre-eclamptic toxemias and eclamptics a marked decrease will be observed.

Age.—According to Tocantins there is no significant change in platelet counts until the age of 60 years, after which age there is a definite decrease.

Numerous other factors influence platelet count levels, namely blood dyscrasias, disorders of the endocrine system, trauma, fractures, operative procedures, but need not be considered in this paper.

Methods of Estimating Platelets

The direct method in which platelets are counted in a counting chamber is similar to that of counting red and white blood cells, the results are estimated per cubic millimeter of blood.

The indirect method is a smear method in which a blood smear is made and stained with a platelet stain, the number of platelets are calculated in relationship to the number of red blood cells.

In this series we chose the direct method, because it appeared simple and is the method employed by the department of hematology in the Montreal General Hospital. Cutaneous blood was used because the seasonal variation is not important. Free-flowing blood was obtained from the lobe of the ear by means of a stab wound obtained by a stylet puncture, which ensured free flow of blood in all cases.

The method used was as follows:

A solution made of:

Sodium citrate	2.5 Gm.
Mercury bichloride	0.005 Gm.
Brilliant cresyl blue	0.5 Gm.
Aqua dist. ad	500 c.c.

This solution was used as a stock mixture. Fresh solution is made up weekly for use in platelet counting. To 40 c.c. of the stock solution add 1 Gm. of fresh powdered urea. In order to cut down the error due to contamination, etc., daily counts were carried out on the solution itself prior to actually counting blood platelets.

Free-flowing blood was obtained by a deep stab wound in the lobe of the ear. The blood was drawn up to the 0.5 mark in a white cell pipette, and the diluting fluid was drawn up to the mark 1. The pipette was sealed with a rubber band and shaken for one minute, and allowed to stand for fifteen minutes. A drop of the solution was placed on the counting chamber and counted in a similar manner to that of counting red blood cells, that is to say five small squares were counted and the total estimated in platelets per cubic millimeter of blood.

Our platelet counts were made by one technician who was trained in the hospital laboratory for this purpose. It was felt that with use of a careful technique carried out by the same technician, the results should be reasonably accurate and consistent.

In order to establish a normal level, thirty nonpregnant women were chosen who were in the same age group as the pregnant patients to be examined. Samples of the blood for examination were obtained two weeks prior to the onset of menstruation, in order to eliminate the fall in platelet level which occurs just prior to the onset of each period. There was considerable variation, the minimum count obtained was 159,000 and the maximum count in this series was 223,000, the average for this group was 182,000.

Tocantins reviewed the work of fifteen authors who had carried out platelet counts by the direct method using cutaneous blood. He found that the minimum count was 174,000, while the maximum was 400,000. The average platelet count in this group was 187,000, which closely approximates our normal series.

In order to eliminate as many common factors as possible which influence the number of platelets, the following precautions were taken: all blood was taken at least two hours after a meal; the exercise factor was constant because

all patients walked about the same distance to the hospital from the street-car; and all patients had been sitting in the waiting room at least one-half hour prior to obtaining the blood. These counts were carried out from March until July. A check was made to determine whether there was any seasonal variation. It was found that counts done in June and July averaged 10,000 platelets lower than those in March and April, this difference does not seem significant. Drugs were not used in these prenatal patients, therefore could not cause any error.

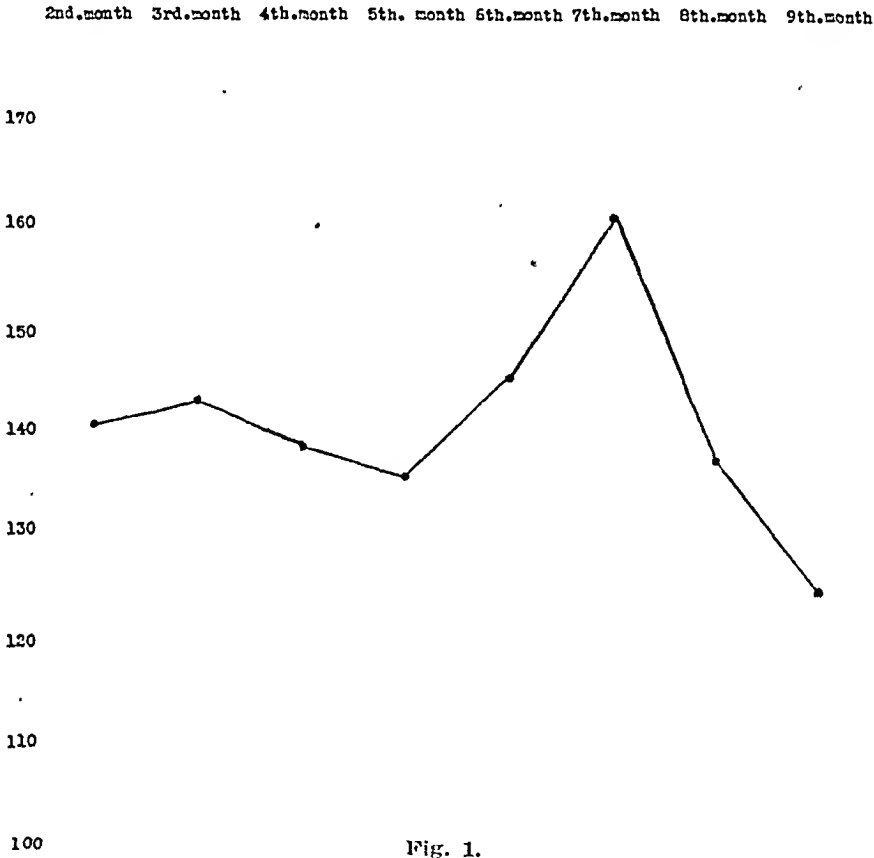


TABLE I. 200 PLATELET COUNTS BY MONTHS SHOWING VARIATION AND AVERAGES

MONTH	VARIATION		AVERAGE
	MINIMUM	MAXIMUM	
Second	61,000	235,000	141,000
Third	55,000	210,000	144,000
Fourth	63,000	207,000	139,000
Fifth	85,000	198,000	136,000
Sixth	60,000	228,000	146,000
Seventh	110,000	237,000	164,000
Eighth	54,000	226,000	138,000
Ninth	56,000	190,000	125,000

Table I and Fig. 1 show the results of 200 platelet counts by months. There is considerable variation in the counts for each period, but the average platelet count is lower than the normal level of 182,000. The curve maintains a fairly even level except for an unexplained rise at the seventh month. The average decrease below the normal level was 40,000. It is interesting to note that in recent work on plasma protein determinations in 600 cases of normal pregnancy, one of us (J. L. M.) noted that plasma proteins appeared to be below normal in this group.

The mean normal plasma protein level is 7.2 grams. In the above series the mean level of plasma proteins during the first trimester was 6.1 Gm., falling to 5.9 Gm. in the last trimester of pregnancy.

There appears to be a relationship between the platelet and plasma protein levels in these two series which may be significant.

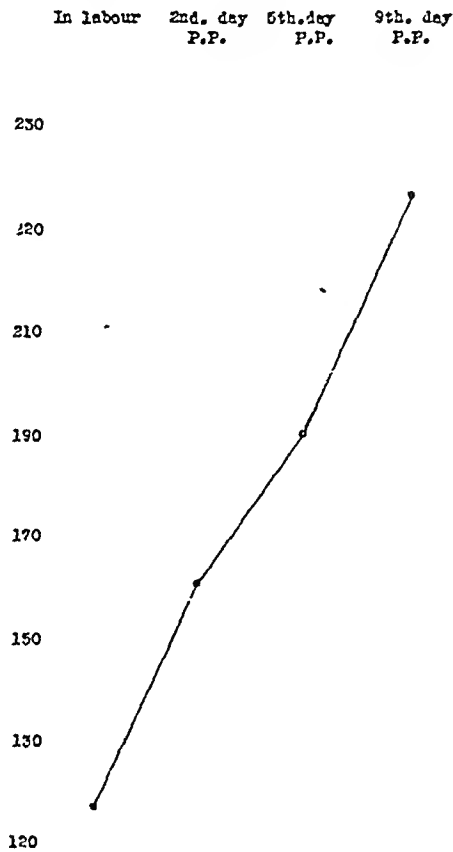


Fig. 2.

TABLE II. PLATELET COUNTS IN LABOR AND SECOND, FIFTH, NINTH DAY POST PARTUM; SHOWING VARIATION AND AVERAGE COUNTS

TIME	VARIATIONS	AVERAGE
In labor	66,000—201,000	124,000
Second day post partum	108,000—223,000	161,000
Fifth day post partum	122,000—277,000	191,000
Ninth day post partum	130,000—301,000	224,000

Table II and Fig. 2 show that blood platelets are very definitely low in early labor, averaging 124,000, rising rapidly to a level of 224,000 by the ninth day post partum. MacArthur again points out that in his series the plasma proteins rose rapidly in the puerperium to a level of 6.95 Gm., again pointing to a relationship between these two factors in pregnancy and the puerperium.

Some authors have stated that a rapid rise in the number of blood platelets predisposes to phlebothrombosis and possibly thrombophlebitis. If this is true the rapid rise, during puerperium of blood platelets would suggest the necessity of early movement and early exercise in the postpartum patient to avoid the above-mentioned complications.

During the period of our investigation, seventeen patients were admitted to the hospital for the treatment of toxemia of pregnancy. They fell into two

groups, the first a group of ten patients with moderate hypertension, albuminuria, and varying degrees of edema. The second group consisted of six cases of severe pre-eclampsie toxemia and one case of eclampsia. This group showed a higher elevation of blood pressure, an increase in the amount of albumin, and a marked degree of edema.

TABLE III. MILD TOXEMIAS

CASE	BLOOD PRESSURE	ALBUMIN	EDEMA	PLATELETS
1	140/110	+	slight	148,000
2	150/100	+	slight	155,000
3	140/ 90	FT	moderate	134,000
4	160/ 90	FT	slight	223,000
5	140/ 90	FT	slight	143,000
6	150/ 90	+	moderate	152,000
7	148/ 90	+	moderate	145,000
8	140/100	+	moderate	154,000
9	140/100	+	slight	153,000
10	138/ 86	+	moderate	145,000

Ten cases of moderate toxemia were studied, and the platelets varied from 134,000 to 223,000, averaging 155,000, which is approximately the same as platelets in the nontoxic group. Unfortunately, plasma protein determinations were not carried out on this group, due to lack of staff, therefore the relationship between the two factors cannot be ascertained.

TABLE IV. SEVERE TOXEMIAS

CASE	BLOOD PRESSURE	ALBUMIN	EDEMA	PLATELETS	PLASMA PROTEINS
1	180/100	+	+	76,000	4.0 Gm.
2	180/106	+++	+++	98,000	4.2 Gm.
3	158/100	++++	+++	72,000	5.7 Gm.
4	190/130	++++	+++	117,000	3.8 Gm.
5	200/140	++++	++	117,000	4.1 Gm.
6	160/100	++++	++	88,000	3.9 Gm.
7	150/100	+	++	120,000	5.5 Gm.

Six severe pre-eclampsie and one eclampsie patient were examined. The platelet counts were significantly lower than in normal or mildly toxic patients. The platelet counts ranged from 72,000 to 120,000 in the seven patients, the average platelet count being 97,000. Plasma protein levels were definitely low, ranging from 3.9 to 5.5 grams.

It was interesting to note that when the plasma protein levels rose or returned to normal, in all cases there was a parallel rise in the number of blood platelets.

In a small series of anemias associated with pregnancy described by Osler, there appeared to be a striking relationship between blood platelet counts and plasma proteins.

On admission, platelet counts in three cases were 48,000, 77,000 and 97,000, respectively, with plasma protein at 3.4 Gm., 3.6 Gm., and 5.2 Gm. The case of Lederer's anemia, on the other hand, showed a platelet count of 300,000, and plasma proteins of 7.2 grams.

It is acknowledged that this group is small, but the observations may be significant and may provide an added diagnostic point in distinguishing between Lederer's and Osler's anemia pregnancy.

A series of forty-five normal pregnant patients was studied to ascertain the relationship between platelet counts and blood loss at delivery. These patients were a group of private patients admitted in early labor.

Sedatives employed were heroin 0.005 milligram, Demerol 100 milligrams, and occasionally, morphine 0.015 milligram. Gas oxygen anesthesia was used at the time of delivery. Pituitrin, 0.5 c.c., was administered intramuscularly following the delivery of the baby, and ergometrin, 0.125 milligram, intravenously, after the expression of the placenta.

The lowest platelet count was 84,000, and the blood loss was 300 cubic centimeters. The highest platelet count was 225,000, with a blood loss of 300 cubic centimeters. The greatest blood loss, namely 700 c.c., occurred in a patient whose platelet count was 203,000.

It is recognized that there are many other factors which play a part in postpartum bleeding, but in this series no relationship between platelet counts and postpartum bleeding could be established.

Comment

There is a great deal of controversy as to the value of blood platelet determinations. There are numerous techniques outlined in the literature and great variations are reported by different authors. However, as Aggeler, Howard, and Lucia point out, if a given method is chosen, all steps carried out carefully, and one trained technician made all the counts, the results obtained should be of value.

Two hundred platelet determinations were carried out on normal prenatal patients.

Two hundred eleven counts were done on patients in labor and during nine days of the puerperium.

Platelet counts were carried out on seventeen toxic patients and four cases of severe anemia of pregnancy.

Conclusions

1. The average platelet count in nonpregnant patients in our series was 182,000.

2. Platelet counts during pregnancy were definitely below the normal level, averaging 141,000.

3. Plasma protein determinations in normal pregnant patients was also found to be below normal, falling from 6.1 Gm. in the first trimester to 5.9 Gm. in the third trimester.

4. Platelet counts in patients in early labor were definitely low, averaging 124,000, followed by a rapid rise in the puerperium, 161,000 on the second day post partum, to 224,000 on the ninth day.

5. There is a parallel rise in plasma proteins during the puerperium to a level of 6.9 grams.

6. In moderately toxic patients there is no significant change in blood platelet counts.

7. In severe pre-eclamptic and eclamptic patients blood platelets are definitely lower than normal, averaging 97,000.

8. Plasma protein levels are also low in this group, ranging from 3.9 to 5.5 grams.

9. In the pernicious anemias of pregnancy platelets and plasma proteins are markedly below the normal levels.

10. No relationship has been established between platelet levels in the circulating blood and the amount of blood loss occurring at the time of delivery.

11. The apparent relationship between plasma proteins and platelets may be significant and further work will be done to include bone marrow punctures to ascertain the value of the above impressions.

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Discussion

DR. PAUL TITUS, Pittsburgh, Pa.—The fact that such a simple thing as change of posture, to the extent of a 20 per cent decrease, is brought about merely by sitting erect from a horizontal position, suggests that fluctuations or deviations from normal cannot be characteristic of disease conditions. Such simple things as seasonal weather changes, eating food, and ingestion of certain drugs are able to cause changes in the blood platelet count. There is widespread difference of opinion about the effect of pregnancy, if any, on the blood platelet count.

The authors have carried out a comprehensive and painstaking study with a considerable series of cases. Despite this, however, they appear to have formed no definite conclusions regarding any clinical significance of variations in blood platelet counts during pregnancy, except that in severe toxemia and in pernicious anemia of pregnancy platelet counts are below normal.

With the uncertainty of what constitutes a normal platelet count, and the information from the authors that such trifling events may cause wide variations from normal, this study seems to demonstrate that blood platelet counts during pregnancy have no clinical application and are of no more than academic interest.

DR. HERMAN B. VAN WYCK, Toronto, Canada.—This is another approach to one of the most important problems the obstetricians face, the problem of the production of the toxemias, and, I believe, in view of the fact that our knowledge of platelets is so uncertain, as well as their origin and function, that we should not be too ready to agree with Dr. Titus that this matter has only academic interest. They may come from the megakaryocytes of the bone marrow or elsewhere. The variation in the toxemias may be evidence of a protective mechanism which in the severest forms of toxemia is failing.

Many of the changes in pregnancy are protective mechanisms. It appears possible that the other explanation of the origin of platelets—the disintegration of the erythrocytes—may explain that we are dealing with a protective mechanism of some sort, and that in the capillary hemorrhage of the severest toxemias mechanism has broken down.

We have recently begun in Toronto to find out what counts we get and we use the direct method. Our findings in normal and mild toxemia pregnancies are substantially the same as Dr. Ward has reported.

It would be interesting to follow the globulin in these platelet variations in the toxemias because we know that globulin increases during the process of immunization, and perhaps the fall in platelet count is related to toxemic conditions in which immunization has failed entirely.

DR. JAMES R. BLOSS, Huntington, W. Va.—Dr. Ward's paper calls our attention to some very significant things. It is true that we do not know much about blood platelets, but one comment that he made regarding the diminution in the number of platelets, the lowering of plasma, and the development of thrombophlebitis seems to me to have something very significant for us.

I had been brought up, as many of you were, upon the importance of rest after delivery. When my associate came back from the Navy he began getting his patients up very early. It seemed to me that if what I had been taught to do, and what I had taught him in the fifteen years before he entered the Navy, were true, we were in for a bad time and would run into many difficulties. He is getting the patients out of bed within eighteen to twenty-four hours. He has not had any cases of thrombophlebitis. The patients delivered by abdominal section are also encouraged to sit up in twenty-four hours. There may be something in this matter of the platelet count being a great help to us in prognosis and care, and since it goes up on the ninth day so markedly, and even such change of posture as getting the patient up, which Dr. Titus calls attention to, may make a change in the blood count. I am wondering about the significance of the platelet count. In the course of time we may be able to make a number of deductions and learn a great deal about the value of this procedure.

DR. WARD (Closing).—I am in hearty agreement with Dr. Titus that the figures outlined in this paper do not prove anything. We were interested in finding out what changes occurred in platelet counts during pregnancy and the puerperium and have presented the results as we found them.

I am glad to know that our findings correspond with the work done by the Toronto group. We propose to continue this work and investigate the relationship between platelet levels, plasma proteins, and protein metabolism during pregnancy.

HYPERTHYROIDISM AND PREGNANCY*

ROBERT D. MUSSEY, M.D., SAMUEL F. HAINES, M.D., AND EMMERSON WARD, M.D.,
ROCHESTER, MINN.

(From the Section on Gynecology and Obstetrics, and the Division of Medicine, Mayo Clinic and Mayo Foundation)

HYPERTHYROIDISM is an uncommon complication of pregnancy. Its reported incidence ranges from 0.03 to 3.7 per cent of all pregnancies, with an average of about 0.2 per cent.¹⁻³ Nevertheless, dangers to the mother and fetus make it important that proper treatment be instituted promptly. Uncontrolled hyperthyroidism not only leads to a high incidence of abortions, but also subjects the mother to all the hazards inherent in thyrotoxicosis. On the other hand, suitable management of hyperthyroidism in pregnancy results in a fetal mortality rate not greatly higher than that of otherwise uncomplicated pregnancy, and also affords control of maternal thyrotoxicosis comparable to that in nonpregnant women. Pregnancy does not seem to alter the course of hyperthyroidism in most cases.

Although some earlier writers have advocated therapeutic abortion in hyperthyroidism, most recent authors are agreed that such a procedure is rarely justified and, in fact, is actually dangerous in that a thyroid crisis may be precipitated. Means⁴ succinctly stated: "It is the thyrotoxicosis, not the pregnancy, which should be interrupted."

In this paper we propose to discuss the management of hyperthyroidism coincident with pregnancy and the results of such management. A brief résumé of the literature of this subject will be presented. Hypotheses of the etiology of goiter and of hyperthyroidism and the interrelationship of hormones concerned in the activity of the thyroid gland do not come within the scope of this communication.

In previous papers⁵⁻⁹ one of us (R. D. M.) has stated that, with rare exceptions, the treatment of hyperthyroidism in pregnant women does not differ from that in nonpregnant women. For exophthalmic goiter, a trial of iodine is indicated; if this fails to control the disease, subtotal thyroidectomy should be performed. In cases of adenomatous goiters with hyperthyroidism, thyroidectomy should be performed after preparation with iodine unless the pregnancy has progressed to the last six weeks, and even then it is indicated if the basal metabolic rate has been more than +50 per cent for a considerable length of time, if there is evidence of myocardial insufficiency, or if the goiter is producing important mechanical symptoms, such as dyspnea due to pressure on the trachea.

Other authors have been in substantial agreement with these conclusions. Yoakam² studied thirty-five patients with hyperthyroidism in pregnancy and decided that conservative treatment, employing iodine, should be tried; then

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thyroidectomy should be performed if necessary. He cited a case in which thyroid crisis was precipitated by therapeutic abortion. With minor differences in management Clute and Daniels,¹⁰ Frazier and Ulrich,¹¹ Bothe,¹² Norrman,¹³ Javert,¹⁴ and Davis¹⁵ followed a similar regimen.

Davis¹⁵ stated that during the first half of pregnancy thyroidectomy entails little risk to mother or fetus, but late in pregnancy he advised postponement of thyroidectomy until the puerperium.

Baumgartner¹⁶ followed a similar plan of treatment, and suggested that near term the use of iodine and cesarean section might be considered; in two cases of recurrent exophthalmic goiter he employed roentgen therapy. McLaughlin and McGoogan,³ Javert,¹⁴ and Kibel¹⁷ observed a high incidence of toxemia of pregnancy in their cases in which hyperthyroidism was associated.

Portis and Roth¹⁸ recommended rest, sedation, and good hygiene without administration of iodine, and reserved thyroidectomy for a small group of cases in which the severity of the hyperthyroidism increased and visceral damage occurred. They stated that the use of iodine might obscure the course of the disease and also might produce iodine fastness, if surgical intervention were decided on later. Interruption of pregnancy was considered to be contraindicated except in unusual circumstances.

Newer Agents Used in Treatment of Hyperthyroidism

Recently two therapeutic agents, thiourea with related goitrogenic drugs, and radioactive iodine, have been introduced for the treatment of hyperthyroidism. Investigation of the goitrogens was begun in 1928 when Chesney, Clawson, and Webster¹⁹ produced hyperplastic goiter and lowered metabolism by feeding a cabbage diet to a colony of rats used for the study of syphilis. Subsequently, four different groups of goitrogens have been identified: cyanides,²⁰ thiocyanates,²¹ certain aniline derivatives related to the sulfonamides,²² and thiourea and its derivatives.^{23, 24}

Of these four, only the last have been applied to the treatment of hyperthyroidism. Astwood,²⁵ in 1943, first reported the clinical use of thiourea and thiouracil. Various workers since then have studied and reported large numbers of cases. Results indicate that in the majority of cases hyperthyroidism can be controlled by thiourea or its derivatives, but there is a high incidence of recurrence of symptoms after administration of the drug is stopped. Thus far, one of the major factors limiting the use of these compounds has been the toxic reactions associated with their administration; the most serious reaction, agranulocytosis, had produced twenty-one known deaths by February, 1946.²⁶ According to Astwood and VanderLaan,²⁷ propylthiouracil has less propensity to produce toxic reactions and the experiences of others tend to confirm this statement.

The production of benign and malignant thyroid tumors in rats by the concomitant administration of thiouracil and 2 aceto-amino-fluorene was reported by Bielschowsky.²⁸ The effect of chronic treatment of adult rats with 0.1 per cent solution of thionracil for three to four months was said by Money²⁹ to have been followed by the development of thyroid adenomas in 100 per cent of animals, and Purves and Griesback³⁰ reported that the long-continued use of thiourea in rats produced thyroid tumors in most of the rats. In two of

thirty rats metastatic lesions of thyroid origin were found in the lungs. Broders and Parkhill³¹ have commented on the similarity between carcinoma of the thyroid and the picture of cellular hyperplasia with numerous mitotic figures in a thiouracil goiter. Hinton and Lord³² have suggested that thiouracil might prove capable of increasing the incidence of malignant lesions in the thyroid. However, in no instance has any accepted evidence been presented that thyroid tumors have been produced in man by thiourea or its derivatives.

The exact place of thiourea and its derivatives in the treatment of hyperthyroidism has yet to be determined. While some clinicians have concluded that these drugs can replace thyroidectomy in many cases of hyperthyroidism, others are of the opinion that their use should be limited to selected patients, who are unfit for thyroidectomy, and to the preparation of patients with hyperthyroidism for operation.

The current clinical usage of these agents at the Mayo Clinic, as stated by Haines and Keating³³ is: "(1) as a total treatment for hyperthyroidism in those cases in which complications prohibit surgical treatment of the disease, (2) as a preoperative treatment in those cases in which the severity of the hyperthyroidism is responsible for an anticipated high surgical risk, or (3) as a preoperative treatment in those cases in which complications increase the surgical risk, especially if temporary relief of hyperthyroidism will bring about some amelioration of the complicating condition."

The mode of action of thiourea and its derivatives is not completely understood. It has been demonstrated that uptake of iodine and production of thyroid hormone by the thyroid are inhibited.³⁴⁻³⁷ Present evidence seems to favor the theory that these compounds interfere with some oxidative enzyme concerned with the synthesis of the hormone.^{38, 39}

Concerning the effect of use of thiouracil and related compounds in the course of pregnancy, a number of experiments with animals gave warning that danger might be encountered. The young of rats fed thiouracil during pregnancy were found to have enlarged thyroid glands; however, subsequent growth and development were normal if no thiouracil was administered after birth.⁴⁰ Administration of thiouracil to young rats caused retardation of growth and other cretinous changes, as well as hyperplastic goiters.⁴¹ It has been shown that administration of thiouracil to lactating women results in a relatively high concentration in the milk.⁴² Its administration to lactating rats caused retardation of growth in the suckling young.⁴³ Hatching of chick embryos was delayed as much as ten days by injection of thiourea into the yolk sac.⁴⁴ Feeding thiouracil to hens caused enlarged thyroids in their chicks.⁴⁵

Several reports of the administration of thiouracil to pregnant women have been published. McGavack, Gerl, Vogel, and Schwimmer⁴⁶ employed thiouracil in a case of pregnancy and adenomatous goiter with hyperthyroidism. Treatment was initiated during the fifth month of pregnancy and continued for five and one-half months. Control of the hyperthyroidism and a normal delivery resulted.

Rose and McConnell⁴⁷ gave thiouracil to a patient with hyperthyroidism; treatment was started when the patient had been pregnant for four months; it was continued for fifteen days and then discontinued for one month; after which time it was given until one week before delivery. The patient was delivered at term of a healthy male infant who gave no evidence of enlargement or dysfunction of the thyroid gland.

Palmer⁴⁸ reported three cases in which thiouracil was administered during pregnancy. In one case administration of thiouracil was started in the fourth month of pregnancy and continued until the ninth month, when it was stopped because the basal metabolic rate was less than +10 per cent. The delivery was uncomplicated and the infant was normal. In another case, the results were inconclusive, and in a third the outcome was not stated.

Eaton⁴⁹ treated thyrotoxicosis in pregnancy with thiourea and thiouracil in two cases. The first patient received the drugs from the third to the eighth month of pregnancy; a healthy child was born without incident. The second patient received thiouracil prior to and during the first month and then during the last seven months of pregnancy. Delivery was by cesarean section because of placenta previa. The female infant had an enlarged soft thyroid, the entire outline of which was readily visible in the neck; the infant was normal otherwise. At the age of three months the infant's growth had been normal and the thyroid was no longer apparent. Eaton suggested that administration of thiouracil be replaced by iodine some weeks before delivery.

Davis and Forbes⁵⁰ reported a case in which a woman 21 years old who was taking 0.2 Gm. of thiouracil daily became pregnant. She continued to take this dose until her sudden and unexplained death in the sixth month of pregnancy. Examination revealed in the mother a hyperplastic thyroid and a soft dilated heart. Examination of the fetus showed an enlarged thyroid. The gland contained no colloid; the acini were enlarged and composed of fairly tall columnar cells, and the small vessels were congested. The authors stated that the fetal thyroid had the general appearance approximating that found in adults with thyrotoxicosis. They suggested that the effect was due to the direct action of thiouracil on the fetal thyroid rather than to the effect of maternal thyrotropic hormone or to an effect of lack of thyroxin from the mother, who was not myxedematous.

Williams⁵¹ gave thiouracil to five pregnant women. Three received thiouracil before and during the entire course of pregnancy, one received it during the last six weeks, and the fifth, during the last month of pregnancy. All six infants, including one set of twins, were in excellent condition at birth, and none had a goiter.

Sexton⁵² reported the cases of two women who were carried through pregnancy by means of thiouracil without untoward effect on the course of pregnancy or on the fetus.

Carns and Poser⁵³ reported a case in which thiouracil was administered from the second to the sixth month of pregnancy, except for one month during which treatment was not followed, although it was advised. It then was given again during the last month of pregnancy. A healthy child was born.

Astwood and VanderLaan⁵⁴ found that, in a series of 100 patients who were treated with propylthiouracil for hyperthyroidism, three became pregnant and were delivered of normal children during the course of therapy.

Vogt⁵⁴ reported a case in which methylthiouracil was given daily until the time of parturition. Although the patient's thyroid enlarged during the treatment, the child's thyroid was normal.

Freiesleben and Kjerulf-Jensen⁵⁵ used methylthiouracil to control successfully the hyperthyroidism of a pregnant patient. Because of complicating heart failure the fetus was removed in the fifth month of pregnancy. The fetal thyroid was hyperplastic.

Experience at the Clinic with thiouracil in pregnancy has been limited to one case.

CASE 1.—This patient, a white woman (gravida ii, para i), 23 years old, was registered in March, 1944, at which time a diagnosis of exophthalmic goiter

was made. The basal metabolic rate on March 23, 1944, was +91 per cent. The patient had been taking Lugol's solution daily for nine months prior to admission, and continued to take it until April 29, 1944. Because of the inadequate response to Lugol's solution, administration of 0.2 Gm. of thiouracil every eight hours was started April 29; on September 13 the dose was reduced to 0.4 Gm. daily, and was omitted November 6, when it was found that the patient was approximately two months pregnant. Administration of Lugol's solution was begun again, and thyroidectomy was performed on Nov. 24, 1944. During treatment with thiouracil the basal metabolic rate had declined from +75 on April 26, 1944, to +24 per cent on Nov. 6, 1944, and parallel improvement in the patient had occurred. When seen in March, 1945, the patient was clinically euthyroid, and had a basal metabolic rate of +12 per cent. She reported later that on June 28, 1945, she gave birth to a normal infant weighing 8 pounds (3.6 kg.), and that both mother and baby had been well.

On the basis of the experiences mentioned in the literature, it would appear that the advisability of using thiouracil during pregnancy is not clearly established. However, children of mothers treated with thiouracil during pregnancy should be observed for a longer time before opinions on this point are formed. To our knowledge, no human infant has been allowed to nurse if the mother is taking thiouracil. On the basis of animal experimentation, one may conclude that such a procedure might result in unfavorable effects on the growth and development of the child.

From such a small series of cases as those reported in the literature, it is difficult to evaluate the results of treatment in regard to the effectiveness of the thiourea and its derivatives in controlling hyperthyroidism during pregnancy. In general, the control in those cases described in the literature was neither remarkably better nor worse than that in a comparable group of non-pregnant women, and there is no reason to assume any unusual difficulty in controlling hyperthyroidism with thiouracil or propylthiouracil in such cases.

Radio-iodine was first made by Fermi⁵⁶ in 1934, shortly after Joliot and Curie⁵⁷ had discovered artificially produced radioactivity. In 1938 Hertz, Roberts, and Evans⁵⁸ employed radio-iodine to determine the concentration of iodine in the thyroid; subsequently wide use has been made of this substance as a tracer in the study of thyroid physiology. In 1942 Hertz and Roberts⁵⁹ and Hamilton and Lawrence⁶⁰ reported that radio-iodine had been used successfully in the treatment of cases of hyperthyroidism. Hertz and Roberts⁶¹ in 1946 published the results of three to five years of study of twenty-nine cases in which hyperthyroidism was treated with radio-iodine. In the same year, Chapman and Evans⁶² reported another similar series of twenty-two cases. The results of treatment in these instances have been encouraging, but it is still too early to predict the future of radio-iodine as a therapeutic agent. Its place in research is well assured. So far no instance in which radio-iodine has been employed in the treatment of hyperthyroidism in pregnancy has come to our attention. One patient whose case was reported by Hertz and Roberts became pregnant subsequent to such treatment. We would be hesitant to use radio-iodine in the treatment of hyperthyroidism in pregnancy until more is known of the extrathyroidal and delayed effects of radio-iodine.

Data on Thirty Instances of Hyperthyroidism and Pregnancy

Mussey, in 1939, reported the results of treatment in thirty-six cases of pregnancy with hyperthyroidism observed at the Clinic from 1923 to 1937, inclusive. In this paper we wish to present data on a similar group of cases from the same clinic from 1938 to 1946, inclusive, a nine-year period in which thirty pregnancies of twenty-nine patients were complicated by hyperthyroidism, for one patient had a recurrent exophthalmic goiter during a second pregnancy. In general, treatment followed the plan outlined by one of us (R. D. M.) which we mentioned in a previous paragraph. An attempt was made to control mild exophthalmic goiter by oral administration of iodine in the form of Lugol's solution; if necessary, thyroidectomy was performed, after preoperative preparation with iodine. Adenomatous goiter with hyperthyroidism was treated by thyroidectomy in *all* cases.

Of the twenty-nine patients, nine had adenomatous goiter with hyperthyroidism; eight of these nine patients underwent thyroidectomy during pregnancy, and one after a spontaneous abortion (Table I). Twenty of the twenty-nine patients had exophthalmic goiter during one pregnancy, and one of these had a recurrence of the exophthalmic goiter with a subsequent pregnancy. In seventeen of the twenty-one instances of exophthalmic goiter thyroidectomy was performed during pregnancy. In sixteen it followed treatment with iodine and in one (Case 1) thiouracil and later iodine were used. In three of the twenty-one instances the thyrotoxicosis was controlled adequately with iodine during pregnancy, and in one thyroidectomy was performed after spontaneous abortion which began before definite treatment of the thyrotoxicosis had been started. In five instances the exophthalmic goiter was recurrent; treatment in four of these consisted of thyroidectomy during pregnancy, and the symptoms in the fifth were controlled by iodine. There were no maternal deaths. In all instances the hyperthyroidism was well controlled when the patient left the clinic.

TABLE I. TREATMENT USED TO CONTROL HYPERTHYROIDISM DURING PREGNANCY*

TREATMENT	EXOPHTHALMIC GOITER	ADENOMATOUS GOITER
Iodine	3	0
Iodine and thyroidectomy during pregnancy	16	8
Iodine, thiouracil and thyroidectomy during pregnancy	1	0
Spontaneous abortion before treatment	1	1
Total pregnancies	21	9
Patients	20	9

*Hyperthyroidism was controlled in all cases when patients were dismissed from clinic.

In ten instances the condition of the mother and fetus at termination of pregnancy is not known (Table II). The results of the pregnancy are known in twenty instances. Sixteen normal infants were born. In two instances, one of exophthalmic goiter and one of adenomatous goiter with hyperthyroidism, spontaneous abortions occurred or started before treatment of the thyrotoxicosis was initiated. In one instance of exophthalmic goiter an abortion occurred eight days after thyroidectomy. In another instance a premature infant born during the eighth month of pregnancy died a few hours after birth; this infant's mother had had a hyperfunctioning adenomatous goiter removed during the third month of pregnancy, and had remained in very satisfactory condition during the rest of her pregnancy. None of the nine infants delivered at the clinic had any thyroid abnormality. The hyperthyroidism of the mothers was known to be controlled at time of delivery in the sixteen instances of full-term pregnancies, one instance of premature delivery, and in one instance of the women who had abortions.

TABLE II. OUTCOME OF PREGNANCY: 29 PATIENTS (30 PREGNANCIES)*

RESULT	EXOPTHALMIC GOITER	ADENOMATOUS GOITER WITH HYPERTHY- ROIDISM	TOTAL
Unknown	8	2	10
Spontaneous abortion before treatment	1	1	2
Spontaneous abortion during treatment	1	0	1
Therapeutic abortion	0	0	0
Child born alive and lived	11	5	16
Child born alive and died	0	1	1
Stillbirths	0	0	0
Neonatal thyroid abnormality	0	0	0
Total pregnancies	21	9	30

*No maternal deaths.

In twenty-one instances the onset of hyperthyroidism antedated the onset of pregnancy; in five the onset of pregnancy preceded the hyperthyroidism, and in four the onset of hyperthyroidism was too insidious to be certain of its relation to pregnancy.

In those twenty-one instances in which the onset of hyperthyroidism preceded pregnancy, the course of the hyperthyroidism apparently was not affected appreciably by the pregnancy in nineteen, whereas in two cases the symptoms of hyperthyroidism were slightly increased during pregnancy. In none was there significant diminution of symptoms during pregnancy, nor any change in the course of hyperthyroidism that could be attributed to the pregnancy.

Ill-effects possibly attributable to thyroidectomy during pregnancy were seen in only two instances. In one case abortion in the third month of pregnancy occurred eight days after thyroidectomy for exophthalmic goiter. In a second case a planned subtotal thyroidectomy was interrupted after removal of only one lobe and the isthmus because of the onset of uterine contractions during the operation; later in the pregnancy the other lobe was resected without incident. The patient went to term and gave birth to a normal infant.

Three representative cases follow:

CASE 2.—A white woman, 44 years old (gravida v, para iii), was seen at the clinic on Jan. 14, 1943; she complained of nervousness and pain at the left costal margin. Three years previously she had noted gradual onset of tiredness, loss of weight, and dyspnea on exertion; these symptoms had persisted without change to the time of examination.

Physical examination revealed a blood pressure of 116/64, a pulse rate of 76 beats per minute, temperature of 98.6° F., weight of 105 pounds (47.6 kg.). The normal weight was 130 pounds (59.0 kg.). The thyroid was slightly enlarged and nodular, skin was warm and moist, and a systolic murmur was heard best over the apex. Weakness, grade 1 (on a grading basis of 1 to 4), was noted. The uterus was the size and consistency expected in pregnancy of three and one-half months' duration. The basal metabolic rates on two occasions were +33 and +26 per cent. Urinalysis, blood counts, serologic tests, and roentgenograms of the chest all gave negative or normal results. A diagnosis of adenomatous goiter with hyperthyroidism and intrauterine pregnancy was made. The patient was given Lugol's solution, and subtotal thyroidectomy was done on Jan. 25, 1943. The pathologist reported that the removed thyroid tissue consisted of multiple hyaline granular degenerating colloid and fetal adenomas in a colloid thyroid. The patient was dismissed, at which time no medication was prescribed. On July 3, 1943, the patient was spontaneously

delivered of a normal female infant weighing 2,520 Gm. Subsequent examinations of the patient at the clinic in November, 1944, and March, 1947, revealed no evidence of thyroid dysfunction.

CASE 3.—A white woman, 29 years old (gravida iv, para iii), was seen at the clinic on Sept. 8, 1942. She complained of heart consciousness, loss of 20 pounds (9.1 kg.), polyphagia, intolerance to heat, weakness of legs, and enlargement of the neck of one year's duration. Her last menstrual period had begun June 11, 1942. Examination revealed blood pressure of 162/70, a pulse rate of 120 beats per minute, and temperature of 99.8° F. Generalized vitiligo was noted; the skin was warm and moist, the thyroid enlarged, and a bruit was audible over it. Weakness, grade 1, of the skeletal muscles was present. Pigmentation of the breasts was increased, and the size and consistency of the uterus were as expected at three months of gestation. The basal metabolic rate was +53 per cent. Blood counts, serologic tests, urinalysis, and roentgenograms of the chest revealed normal conditions. A diagnosis of exophthalmic goiter and intrauterine pregnancy was made. Before any treatment was started the patient began to bleed from the vagina and, on Sept. 10, 1942, she was admitted to the hospital where she passed decidual tissue. Administration of Lugol's solution was started at this time, and on Sept. 23, 1942, subtotal thyroidectomy was performed. The pathologist reported parenchymatous hypertrophy with thyroiditis, grade 2. The patient was advised to continue to take Lugol's solution indefinitely, and was advised against pregnancy for one to two years. On dismissal Oct. 5, 1942, her general condition was good.

CASE 4.—A woman, 30 years old (gravida i), was seen at the clinic on Aug. 12, 1942, with a chief complaint of nervousness and fluttering of the heart. Thyroidectomy had been done for thyrotoxicosis four years previously. The last menstrual period had occurred in March, 1942; some vaginal bleeding had appeared five days before she came to the clinic. Examination revealed an apprehensive and nervous patient with slight exophthalmos, a diffusely enlarged thyroid, enlarged heart, a pulse rate of 110, blood pressure of 132/88, and temperature of 98° F. The size of the uterus was that expected at four months of gestation. The basal metabolic rate was +53 per cent; the concentration of cholesterol was 277 mg. per 100 c.c. of plasma; the value for hemoglobin was 10.75 Gm. per 100 c.c. of blood. There were 4,130,000 erythrocytes and 7,400 leukocytes per cubic millimeter of blood, and the serologic test and urinalysis revealed normal conditions. Slight prominence of the conus was noted in the roentgenogram of the chest. A diagnosis of recurrent exophthalmic goiter and intrauterine pregnancy was made. The patient was given Lugol's solution. The basal metabolic rate fell to +26 per cent by Aug. 22, 1942. Subtotal thyroidectomy was performed Aug. 24, 1942. The pathologist reported parenchymatous hypertrophy with thyroiditis, grade 2. On Jan. 13, 1943, spontaneous delivery of a normal male infant weighing 3,210 Gm. occurred. In May, 1943, the patient was found to have developed myxedema; treatment with desiccated thyroid restored her to normal health.

Summary and Comment

The recent literature concerning hyperthyroidism in pregnancy was reviewed. Thiouracil and related drugs have been used to control hyperthyroidism in pregnant women in a small number of cases reported in the literature. The occurrence of hyperplastic thyroids in a few of the fetuses would call for caution in the use of these drugs in pregnancy, although in several instances they have been successfully used without demonstrable harmful effects. Of the

goitrogenic drugs so far employed in treatment of hyperthyroidism in pregnancy, reports seem to indicate that propylthiouracil can be used with greatest safety to the mother.

In thirty instances in which the patients received treatment at the Mayo Clinic hyperthyroidism complicated pregnancy. Recommended treatment of the hyperthyroidism included oral administration of Lugol's solution and thyroidectomy for hyperfunctioning adenomatous goiters, and Lugol's solution plus thyroidectomy, if needed, for exophthalmic goiter. Pregnancy did not seem to influence the course of hyperthyroidism in most cases. Likewise, proper treatment of the hyperthyroidism allowed the pregnancy to proceed normally.

It is our opinion that the standard treatment of hyperthyroidism by iodine and thyroidectomy can be carried out safely in the great majority of cases of hyperthyroidism complicating pregnancy. Subsequent experience will afford more information about the relative advantages or disadvantages of treatment with antithyroid drugs in these cases. We have not had experience with the use of radio-iodine in pregnant women. At the moment it would seem desirable to learn more of the possible effects of radio-iodine before using it for treatment of hyperthyroidism in pregnant women.

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Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—Dr. Mussey has presented a group of patients handled by medical management for a short period of time followed by a rather high incidence of surgical intervention. The results that have been obtained at the Mayo Clinic speak for themselves, and they are good. The only question in my mind is whether equally good results might be obtained by a complete medical management. In our clinic we have favored the avoidance of surgical intervention except in those cases where manifestly the patient is going downhill rapidly in spite of what we can do medically. We have not had much experience with the newer drugs mentioned by Dr. Mussey. We have used thiouracil in a few cases with good results. We caution against accepting the results obtained in experiments on rabbits and transferring them to the solution of human problems because usually the dosage used in the rabbits are very much higher than would be used therapeutically in the human being.

In both of the cases where we used thiouracil the mother went along perfectly well, the hyperthyroidism decreased and the fetus showed no damage; so it would seem that, so far at least, not a great deal of damage is to be expected from these drugs, in spite of the fact that they should be carefully watched while being administered.

In the consideration of hyperthyroidism complicating pregnancy we should take into account the differences in thyroid activity in different parts of the country. The thyroid behaves differently in the Great Lakes district than it does on the seacoast and things that apply in one part of the country for the therapeutic use of drugs do not necessarily apply in other parts of the country.

There is no question but that the thyroid is stimulated to increased activity in all cases of pregnancy, or at least physiologically it should be so. It is part of the physiological-clinical dystrophy which is really what pregnancy is, a change in the activity of the glands of internal secretion, and the important thing is to realize that this physiological change is reversible at the end of pregnancy, and in most patients returns to normal. There may be also an expression of dysfunction of the thyroid gland which is due to a dysfunction of some other gland, either the ovary or the hypophysis. That should not be overlooked.

It is also important to realize that with either hypo- or hyperthyroidism there is a tendency to abortion. It is very difficult for a surgeon to estimate how much of the gland to remove in order to get just the right balance. In the nonpregnant woman that does not make so much difference, but in the pregnant woman if too much is removed it may result in the emptying of the uterus. In any of these patients upon whom it is contemplated to operate, I believe that some measure should be taken to reduce the irritability of the uterus. I favor the use of corpus luteum extract.

There is a correlation between hyperthyroidism and hypergravidarum, but many cases that have come into our clinic have been found to be associated with both and treating the hyperthyroidism has resulted in an improvement of the hyperemesis. It is also important to realize that the hyperthyroidism is frequently associated with toxemias of pregnancy. What this relationship is is not too clear, but the increase in the end products of metabolism is obvious, we feel, which throws an extra load on the kidney and may be partly responsible for the toxemia.

I cannot quite accurately quote the number of cases that we have had in our clinic, but in general I should say that we have had about two dozen cases which would correspond pretty well with Dr. Mussey's cases. None of our patients had severe enough hyperthyroidism to require operation. One patient who entered the clinic as a hyperemesis gravidarum had a basal rate of +111, and one a rate of +109. The first case was carried through two pregnancies successfully. The latter had had therapeutic abortion for hyperemesis gravidarum at a good clinic in Chicago, and was sent to us for similar treatment, but recovered under Lugol's solution and bed rest. She was put to bed in September and we delivered the woman on February 4. Lugol's solution was stopped occasionally when the toxic symptoms would increase. There was a normal baby, and within two or three days her basal rate was down less than 10. We then sent her about six weeks later to the surgeon who had advised operation, and he said at that time that she did not need operation for exophthalmic goiter which he had said should have been done during her pregnancy.

I think it is important to realize that with careful management, by skillful surgeons, it is possible to remove parts of the thyroid gland in these patients with hyperthyroidism without producing an undue number of abortions, but that in unskillful hands there would be more abortions. It should also be remembered that with medical management a large percentage of these patients will be carried through pregnancy without aborting, without serious damage, and who will then return to a normal nonhyperthyroidism state.

DR. MUSSEY (Closing).—It occurred to me that perhaps what Dr. Falls said about thyroid activity developing in certain areas of the country may be the reason that a larger proportion of the hyperthyroid cases in the Great Lakes area can be controlled medically than we have found possible. An effort is made to control these patients with Lugol's solution, but often the rate is not controlled as one would wish; in such cases damage to the heart is quite insidious, and if one carries the patient too far on medical management the damage is irreversible. For that reason when the basal metabolism rate has been quite high and when it is brought down, one should be careful not to carry the patient too far on Lugol's solution and then find that it is no longer effective. I have a feeling that the hyperemesis in these patients was a symptom of the hyperthyroidism rather than the hyperthyroidism developed because of the hyperemesis.

IMMEDIATE POSTPARTUM HEMORRHAGE DUE TO RETAINED SECUNDINES*

B. H. CARROLL, M.D., H. H. MEIER, M.D., AND O. H. STONE, M.D., TOLEDO, OHIO
(From the Department of Obstetrics and Gynecology, Mercy and Toledo Hospitals)

EXCESSIVE blood loss in the third stage of labor is the forerunner and the cause of much of our maternal mortality and morbidity.¹⁻³ Although age, parity, type of labor, use of instruments, and many other factors have some predisposing influence upon immediate postpartum uterine hemorrhage, we believe that the most frequent cause of postpartum uterine bleeding is faulty separation or retention of parts of the secundines. The purpose of this paper is to record the blood loss, the clinical course, and the treatment of 115 private patients in whom retained placenta, membranes, or both was the cause of the hemorrhage.

Materials and Methods

The observations were made upon 115 private patients in whom portions or all of the placenta and membranes were retained. These cases were collected consecutively without selection. In each case the blood loss was measured and correlated with various features of the patient's postpartum clinical course.

Method of Measuring Blood Loss.—In collecting blood we use a thin metal plate designed for patients who are delivered in stirrups. The section under the patient is 14 inches wide and 7 inches deep with a central groove for collection and direction of blood (Fig. 1). At the table edge the plate drops 4 inches at a 45° angle. At this angle it accommodates to the give of the table pad, and yet fits the patient closely. The plate is then leveled and curbed to prevent overflow. Two openings are placed for drainage of blood and fluids. A wing guide is so attached that either opening may be closed. A 500 c.c. jar is attached at each opening.

Usually the plate is easily pushed under the patient. An Allis forceps is attached to the leg drape for use in turning the guide. After fluids start draining, neither the plate nor the forceps tip is sterile and the utility nurse must change the bottles.

Episiotomy blood is collected in jar No. 1. When the head distends the vulva the guide is turned to direct the waters, which usually follow the baby, into jar No. 2 or the floor basin. Following delivery, collection of blood is continued in jar No. 1. In case the blood loss exceeds 500 c.c., the utility nurse attaches another jar. Occasionally the plate is not placed under the patient until after delivery of the baby.

To the total amount of blood collected we add 25 c.c. to account for spill, sponges, and so forth (Fig. 2).

Removal of Retained Tissues.—When the uterus is not contracting properly and bleeding is continuing with no sign of abatement, we remove manually any tissue that is retained within the uterus. This may be the whole placenta and membranes or pieces of either that are responsible for relaxation of the uterine muscle. In removing the intact placenta and membranes, we follow the technique as described in textbooks. When pieces of tissue are to be removed, a double layer of gauze is arranged over the first two fingers and folded back over the thumb. This enables the operator to separate and to obtain a more secure

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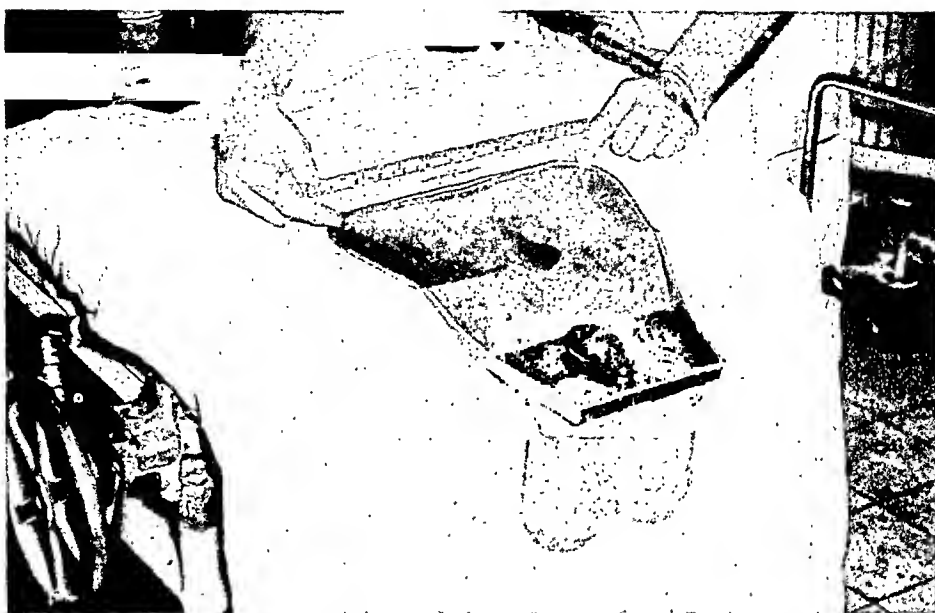


Fig. 1.—View of plate on table, showing incline, wing guide, and containers.

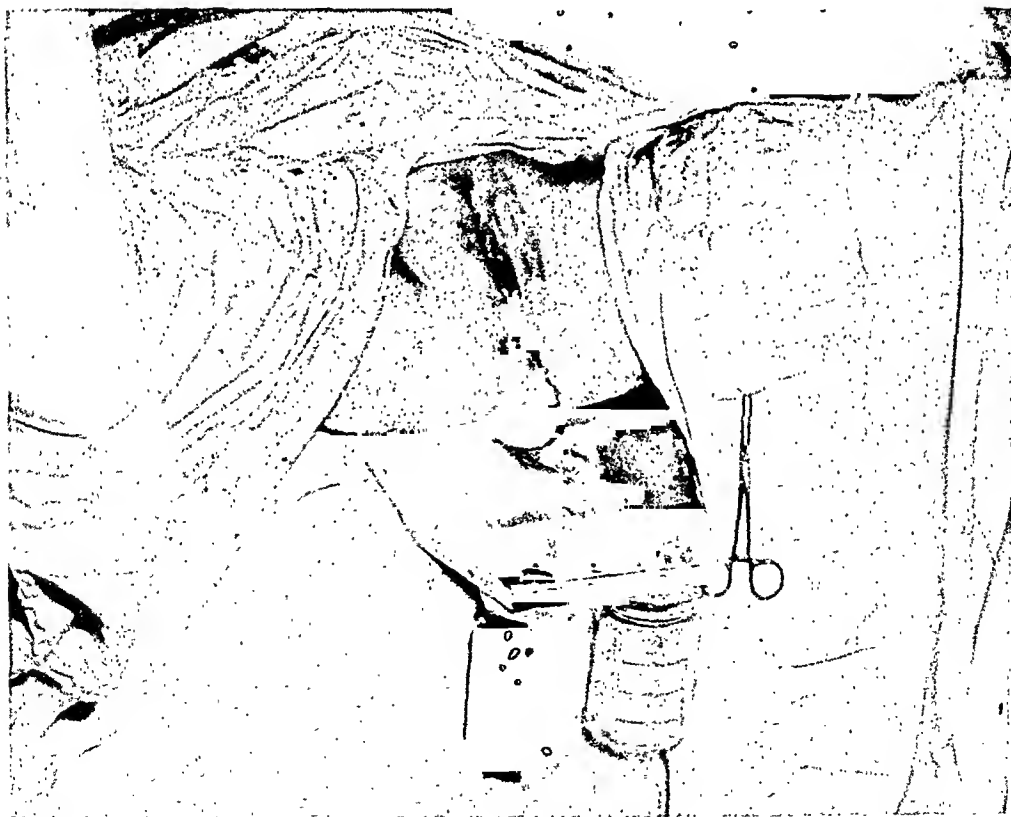


Fig. 2.—Delivery completed. Blood loss accurately measured.

grasp of the retained tissue. The hand is inserted into the vagina and the two fingers and thumb, covered with gauze, are passed through the cervix into the cavity of the uterus. Following removal of tissue, the uterine cavity is routinely wiped with gauze.

Results

Blood Loss.—The patients were arranged in four groups based on the amount of measured blood lost immediately following delivery. Table I.

TABLE I. BLOOD LOSS BY GROUPS

	GROUP I	GROUP II	GROUP III	GROUP IV
AMOUNT, IN C.C.	0-500	500-1,000	1,000-1,500	1,500-2,000
No. of patients	57	39	13	6
Total—115 patients				
Average blood loss	320 c.c.	665 c.c.	1,290 c.c.	1,633 c.c.

Group I, with a blood loss of less than 500 c.c., had fifty-seven patients, averaging a blood loss of 320 c.c. Group II, 500 to 1,000 c.c., had thirty-nine patients, averaging a blood loss of 665 cubic centimeters. Group III, 1,000 to 1,500 c.c., had thirteen patients with an average loss of 1,290 cubic centimeters. Group IV, 1,500 to 2,000 c.c., had six patients with an average blood loss of 1,633 cubic centimeters.

The time after delivery when the retained tissues were manually removed was determined by the character and amount of the bleeding. In all cases, the procedure was done within thirty minutes after delivery. Group I, in which blood loss was not excessive, was composed largely of patients whose placenta was held in the cervix by adherent membranes or of patients in whom it was known that large pieces of placenta or membranes were retained. Removal of these tissues was followed by cessation of bleeding.

In Group II, where blood loss averaged 665 c.c., there was often some delay in manual removal of the tissues while more conservative methods for control were being tried. During this time the patients continued to lose blood. Removal of the retained tissue again promptly stopped bleeding. We believe these uteri should have been emptied earlier. The same holds true for Groups III and IV.

Following removal of the retained tissue and the wiping of the uterine cavity with gauze, it was found that the uterine muscle contracted. No cases of atonic uteri have been encountered following this procedure. We believe that comparatively small pieces of tissue may cause relaxation, while a clean uterine muscle contracts promptly and controls bleeding. During the puerperium the uteri underwent prompt involution. There were no cases of delayed postpartum hemorrhage.

Clinical Studies.—The summary of the various clinical studies is shown in Table II.

TABLE II. CLINICAL DATA

	GROUP I 0 TO 500 C.C.	GROUP II 500 TO 1,000 C.C.	GROUP III 1,000 TO 1,500 C.C.	GROUP IV 1,500 TO 2,000 C.C.	TOTAL AVERAGE
115 PATIENTS	57 PATIENTS	39 PATIENTS	13 PATIENTS	6 PATIENTS	
Shock	0	0	1	0	0.8%
Uterine pack	0	1	0	0	0.8%
Late hemorrhage	0	0	0	0	0%
Chemotherapy	1	3	2	2	8 Pts.—7%
Morbidity	0	3	0	1	4 Pts.—3.4%
Mortality	0	0	1	0	0.8%
Average hospital days	7.5	8	8	9	8

Shock occurred in one patient who had lost 1,375 c.e. of blood. She responded promptly to plasma and blood.

Only one patient was packed. This was used as an aid to support the uterus while repairing a vaginal laceration. Immediately following repair the pack was removed.

There were no cases of delayed or late postpartum hemorrhage.

Chemotherapy was used for eight patients. Sulfonamides were used four times prophylactically and combined with penicillin in four patients who had elevated temperatures. The treatment was effective in all cases.

Four patients ran a temperature of 100.4° F. on two successive days. In two of these the morbidity was attributed to pelvic inflammation, a third sustained a gastroenteritis on the sixth postpartum day and the fourth, who had lost 1,800 c.e. of blood, had pyrogenic transfusion reactions. These four patients made prompt recoveries.

The one death was due to eclampsia. Postmortem examination showed extensive acute necrosis of the liver.

The average number of hospital days was eight. The longest stay was ten days and the shortest six days. With the one exception, every patient went home after being ambulatory for two or more days.

Transfusion.—The percentages of cases in which transfusions were given are shown in Table III. Also the antepartum and postpartum hemoglobin findings are shown.

TABLE III. TRANSFUSIONS AND HEMOGLOBINS

	GROUP I 0 TO 500 C.C. 57 PATIENTS	GROUP II 500 TO 1,000 C.C. 39 PATIENTS	GROUP III 1,000 TO 1,500 C.C. 13 PATIENTS	GROUP IV 1,500 TO 2,000 C.C. 6 PATIENTS	TOTAL AVERAGE
Transfusion	4%	49%	100%	100%	33.0%
Antepartum hemo- globin	73%	73%	74%	74%	73.5%
Postpartum hemo- globin, 6 weeks	70%	75%	74%	74%	73.2%

There was a sharp increase in the number of transfusions in each group. Four per cent in Group I, 49 per cent in Group II, and 100 per cent in Groups III and IV. Groups II, III, and IV make up one-half of the patients, and these received 95 per cent of the transfusions. The 4 per cent transfusions in Group I were given to patients who had an antenatal anemia. Group II had a transfusion rate of 49 per cent. Many of these transfusions were not given until the second day. Although the average blood loss in this group was only 665 c.e., we feel that more of these patients should have received blood much earlier. In Groups III and IV with loss of over 1,000 c.e., the transfusion was started in the delivery room, often before the hemorrhage was controlled. These patients were not moved until their blood pressure was stabilized, the pulse rate 100 or less, and they had reacted from the anesthetic.

The slightly lower postpartum hemoglobin in Group I, as compared to the antepartum value, suggests that more transfusions were indicated and that postpartum antianemic medication was not sufficiently stressed in this group. In the remaining groups, the hemoglobin values at six weeks post partum were equal to or higher than the antepartum values.

Nursing.—The effect of hemorrhage on the ability of the patient to nurse is shown in Table IV.

It is of interest to note that in 68 per cent of these mothers the babies were entirely breast fed at the time of hospital discharge. From Group I to Group

TABLE IV. NURSING AT END OF EIGHT DAYS

GROUP I 0 TO 500 C.C. 57 PATIENTS	GROUP II 500 TO 1,000 C.C. 39 PATIENTS	GROUP III 1,000 TO 1,500 C.C. 13 PATIENTS	GROUP IV 1,500 TO 2,000 C.C. 6 PATIENTS	TOTAL AVERAGE
78%	69%	54%	50%	68%

IV there was a progressive decline in the ability of the patient to nurse, regardless of early transfusion. This may be the manifestation of a defense mechanism resulting from the sudden hemorrhage.

Discussion

We believe that accurate objective measurement of blood loss is a valuable and essential aid in obstetrics. The customary method of estimation is notoriously deceiving and inaccurate. With accurate measurement, the obstetrician will not be surprised by the sudden manifestation of a rapid pulse and falling blood pressure which occurs in the late or critical period, when postpartum blood loss has been excessive. We use accurate measurement of blood loss as an early objective sign which sharply identifies the condition of the patient and also justifies early removal of retained tissues to control uterine bleeding. With our plate, 500 c.c. jars are used. When 500 c.c. of blood have been collected, the operator must realize that his patient is now in the abnormal or danger zone.

Our studies show that blood loss over 500 c.c. is associated with an increased number of clinical complications. With one exception the morbidity, mortality, shock, and need for chemotherapy occurred in patients who had lost more than 500 c.c. of blood. Moreover, blood loss over 500 c.c. was associated with a decreased ability of the mothers to nurse their infants. These findings emphasize the need for accurate objective measurement and control of blood loss during delivery and immediately post partum.

In each of the 115 cases studied we found the bleeding associated with retention of placenta or membranes or both. In Group I the entire placenta or large portions of it were retained. In the remaining groups smaller pieces were retained. In Group I the evidence of retained tissues was more obvious. Consequently, they were removed earlier with the resultant relatively low blood loss in this group. In the remaining groups the retention of secundines was manifested by continual blood loss, often augmented by spurts on contraction and pressure.

When pieces of placenta and/or membranes are retained, when blood loss exceeds 500 c.c., and when the uterus fails to contract, we feel that manual removal of retained tissue is indicated. We wish to emphasize that manual removal should not be practiced routinely or indiscriminately. We believe that standard procedures in the conduct of the third stage of labor, such as administration of pituitrin following delivery, gentle massage of the uterus, and occasional modified Credé should always be followed. In the presence of hemorrhage when these measures fail, manual removal of retained tissues will allow the uterus to contract properly and arrest bleeding.

In our cases manual invasion of the uterine cavity was not associated with a high incidence of morbidity. Infection of the uterine cavity did not follow this procedure and we feel, as others have found,^{4, 6} that infection is more likely to develop where retained pieces of tissue are left in the uterus.

A real and noticeable clinical response was observed when the blood loss was promptly replaced. Thirty-three per cent of the patients were transfused. Yet we feel more transfusions could have been given with benefit. The therapeutic action is both prophylactic and curative.

Conclusions

1. Accurate measurement of postpartum blood loss, as studied in 115 patients, was found to be a reliable, informative procedure. Measurement furnished an early and valuable objective sign for use in the treatment of immediate postpartum uterine bleeding.

2. Retained tissue was the cause of the immediate postpartum uterine hemorrhage in all of these cases. Early manual removal of this retained tissue permitted normal contraction of the uterus and arrested hemorrhage.

3. No ill-effects were noted from early careful invasion of the uterus.

4. An accurate knowledge of excessive blood loss demands early and more frequent transfusions.

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Discussion

DR. R. GORDON DOUGLASS, New York City.—During the past two decades mortality caused by various types of toxemia has shown a progressive decrease. The incidence of eclampsia is now only a fraction of what it was formerly. Prophylactic and early employment of chemotherapeutic agents has eliminated to a large extent serious illness caused by puerperal infection. The third of the triad of major causes of maternal mortality, i.e., hemorrhage, now constitutes the most important cause of maternal morbidity and mortality.

The treatment of hemorrhage from the point of view of both control and restoration of blood volume has also been improved. Transfusion has been made a safer procedure by the establishment of blood banks and newer techniques of compatibility. It is, however, undoubtedly true that transfusion and the control of hemorrhage are often commenced too late.

Dr. Carroll and his associates are to be complimented on reviving interest in the accurate measurement of blood loss during the latter part of the second stage of labor and during the period following the birth of the baby. During the month of August Dr. Carroll's apparatus was employed in seventy unselected cases delivered in the New York Lying-in Hospital; fifty-seven of these patients could be classified in the author's group I, with an average blood loss of 213 c.c.; twelve were in group II with an average blood loss of 645 c.c.; and one was in group III with a loss of 1,235 c.c. It is significant to note that the measured blood loss nearly always exceeded, and on occasions greatly so, the estimated loss. This error was not confined to the junior members of the staff.

The early signs of shock are frequently preceded by a period of procrastination when inadequate measures are employed to combat bleeding. On too many occasions during con-

sistent, but what appears to be insignificant bleeding, the doctor assumes an attitude of expectancy steadfastly maintaining confidence in the physiologic function of the uterus. The most experienced and capable individual will, at times, underestimate blood loss until heroic measures become necessary.

The author's apparatus is simple to employ, measures accurately and, most important, the amount of blood lost at any given time is immediately apparent.

I agree with Dr. Carroll that early intervention by manual removal of retained products, when bleeding persists, should be performed before an excessive blood loss occurs. Intravenous ergonovine during the procedure has in my opinion aided in the prompt retraction and contraction of the relaxed uterus.

In my brief experience with Dr. Carroll's apparatus minor disadvantages have become apparent. First, it is somewhat cumbersome to handle, and also adds another procedure from a nursing point of view in cleansing and sterilizing. Second, the 4-inch drop at an angle of 45° brings the plate in such a position that it may interfere with downward traction such as may be necessary in delivering the shoulders, during some forceps operations and breech extractions. The first objection cannot be sustained validly, while the second could be corrected without detracting from its value by a modification in design. Minor structural changes, if produced commercially, would prolong its period of usefulness.

Shock is a relative term. The authors record nineteen patients with a blood loss of more than 1,000 c.c. and in six of those cases the loss exceeded 1,500 c.c., yet they report only one patient manifesting signs of shock. It would appear to me that if a more liberal interpretation of the term were employed, many more patients would have been classified as having shock. With a more realistic approach and the early application of remedial measures based on up-to-the-minute information on blood loss, the number of patients in impending shock should be greatly reduced.

The reported morbidity (3.4 per cent) in a group of patients where manual removal of retained products was necessary is exceptionally low. If temperatures were recorded every four hours during the observed period of the puerperium the figure becomes even more significant. If patients were classed as morbid who had an elevated temperature on any two days rather than consecutive days, the morbidity would undoubtedly be considerably higher.

The number of patients in whom prophylactic or therapeutic chemotherapeutic agents were employed was small. The authors are reporting on their personal experience with private patients. On a ward service with young and less experienced operators I feel confident that these agents should be employed more frequently.

The relatively low hemoglobin percentage reported both ante partum and post partum is somewhat surprising. The low antepartum determinations might be explained on a basis of hydremia, however, this explanation would not account for the low reading six weeks post partum. It would appear that the more liberal use of transfusions as suggested by the essayist, and iron therapy during pregnancy as well as following delivery, might have improved these results.

I would like to emphasize again the advantage of the authors' simple apparatus that efficiently records blood loss that is at all times apparent. Pastore has described an apparatus that is accurate and meets these requirements. Its routine employment, however, is limited by its complexity. The use of any device for this purpose may appear cumbersome and in many instances unnecessary. I am, however, completely in agreement with Dr. Carroll that if used routinely the unpredictable hemorrhage can be detected earlier than is otherwise possible and remedial measures employed before the life of the patient is endangered.

DR. G. D. ROYSTON, St. Louis, Mo.—I agree with Dr. Douglass that the actual blood loss is often greater than is supposed to occur, for too many of these patients are treated by watchful hopefulness and too much time is lost before active treatment is instituted.

I was rather surprised at the high percentage of hemorrhages occurring in these cases, and that nothing was said about the cause of them except the retention of products. In the Washington University Clinic where we employ all forms of analgesia, we feel very definitely

that the anesthetic employed has a very definite bearing upon the amount of blood loss. We have found that ether is the most common offending agent, that either not enough was given to relieve pain or else too much was given. For the purely normal case we usually employ chloroform, and we feel that more attention should be given to teaching anesthetists how to give it properly instead of scaring them to death and drowning the patient with an anesthetic when an obstetric dose is all that is needed.

DR. JAMES K. QUIGLEY, Rochester, N. Y.—I believe that Dr. Carroll's paper is particularly valuable today, for if we are to look for a lowered death rate it must come from the cases of hemorrhage. In a statistical study for twelve years we have found that deaths from most causes including sepsis and toxemia are pretty well controlled, but deaths from hemorrhage have not decreased. An accurate determination of blood loss is important. The apparatus I use is a very simple plate, not as elaborate as Dr. Carroll's. We simply slide that under the patient and then wheel around a liter glass jar to measure the blood loss. The value of an accurate measurement of blood loss is that we can anticipate the necessity for blood replacement. Symptoms of blood loss such as rising pulse and falling blood pressure lag behind the actual loss, and if we depend upon symptoms alone, we will often find that the most valuable time has passed in which to give transfusions. Williams said the most common cause of postpartum hemorrhage was mismanagement of the third stage of labor. We had two cases in our twelve-year study in Rochester where one patient died in forty minutes and the other in about thirty minutes, in which time the fundus had ballooned, because it was not watched. I think we sometimes hesitate too long to invade the uterus if there is any question of retained tissue, and Dr. Carroll's paper has shown that there is little danger in removal of retained secundines.

DR. EDWARD L. CORNELL, Chicago, Ill.—I believe the greatest cause for postpartum hemorrhage is watchful neglect: manipulating the uterus immediately after delivery of the baby, neglect in using pituitrin and/or ergotrate, and waiting to see how much the patient is going to bleed before determining to interfere. I think the technique should be pituitrin as soon as the head is born, ergotrate as soon as the body is born, and leaving the uterus alone without manipulations. As soon as the baby is separated and the patient shows any signs of bleeding, the uterus is entered or the placenta is removed from the vagina either by early extraction or a combination of early extraction and manual removal. It is a great mistake to wait to see how much blood the patient is going to lose before one interferes. If your hospital technique is good the chances of getting infection of the uterus is minimal. If your patients are becoming infected after invading the uterus, there is something wrong with your technique at the hospital.

DR. IRVING W. POTTER, Buffalo, N. Y.—I was very glad to hear Dr. Royston speak as he did about the anesthetic, and I was particularly pleased to hear him speak so frankly about chloroform. We must teach these young men to come back to its use. We all know about the use of ether.

One other feature has not been mentioned today which is very important. It is that these patients are kept under an anesthetic altogether too long. I mean they are brought into the operating room or the delivery room thoroughly anesthetized, and that procedure has been carried out in an anteroom and no one knows how long she has been under the anesthetic. If the operator will tell his anesthetist not to start the anesthetic until he is ready, he will have very much better results with the anesthetic and fewer times that he will be worried about his patient. Let the anesthetist wait for you to start.

DR. JAMES R. BLOSS, Huntington, W. Va.—I would like to ask Dr. Carroll what he used for the preliminary analgesia. Also, how many of these patients had caudal or spinal block?

DR. LEROY A. CALKINS, Kansas City, Kansas.—I agree with Dr. Carroll in every single particular that he has brought out, and I want also to emphasize what Dr. Royston

and Dr. Potter have said. I think we have paid far too little attention to that phase of blood loss in the third stage of labor.

Further, I would like to amplify what has been said by several speakers with reference to this question of estimation of blood loss. The "estimator" cannot accurately estimate blood loss. He can, however materially improve the accuracy of his observations if he will, every six weeks, conduct an "estimation quiz." Someone in our group takes three sheets, on which there is a known amount of blood on each, and the rest of us try to estimate that amount of blood.

DR. CARROLL (Closing).—We have tried to limit this paper to a discussion of postpartum bleeding due to retained tissue. As stated, postpartum uterine bleeding may be influenced by other causes. The anesthetic used may be a contributing factor in hemorrhage. Most of these patients received nembutal and demerol as an analgesic and were delivered under ether or nitrous oxide and oxygen anesthesia. A few cases were delivered under caudal or low spinal. We could not directly associate faulty separation of the secundines and bleeding with any anesthetic agent.

Ergotrate was given routinely after delivery of the placenta. There were no cases of delayed or late postpartum hemorrhage in this group of patients.

The state of impending shock is difficult to identify. We feel that when a patient has lost 500 c.c. of blood she is definitely in the danger zone. If the blood loss reaches 700 c.c. we give plasma immediately. In this group of patients, whose blood loss was between 500 and 1,000 c.c., 49 per cent were transfused. If the patient loses 1,000 c.c. of blood, she is routinely transfused.

We wish to point out the importance and practicability of measuring blood loss and its relation to treatment of the patient. The method used for measuring is optional.

FACTORS IN THE TREATMENT OF CHORIONEPITHELIOMA*

ALBERT W. HOLMAN, M.D., AND ELIZABETH H. SCHIRMER, M.D.,
PORTLAND, ORE.

OUR recent study of hydatid mole and chorionepithelioma on the Pacific Coast convinced us that there is confusion in the minds of many physicians as to the relationship of these two conditions, and as to the best methods of treating them. This doubt springs primarily from ignorance concerning the origin and course of hydatid mole and of chorionepithelioma; and is accentuated by vague pathologic classification and terminology.

Adenoma, adenoma destruens, chorio-adenoma, chorioma, chorionepithelioma, carcinoma, Ewing's syncytial tumor, malignant chorionepithelioma, penetrating adenoma, malignant mole, syncytioma, and syncytial endometritis are terms used by physicians in answer to questionnaires in our recent survey.

Chorionepithelioma is a misleading term and should be discarded. Epithelioma is applied to carcinoma of dermoid origin and, through usage, has become attached to epidermoid carcinoma. Chorionepithelioma is really choriocarcinoma and, depending upon rapidity of growth, cell type, pattern and invasiveness, should be called choriocarcinoma, Grades I to IV.

Choriocarcinoma is a malignant change of the trophoblastic tissue; both the Langhan's and syncytial layers may be involved.

Syncytial cells persisting after miscarriage or full-term pregnancy in sufficient quantity to give a persistently positive Friedman test, must be considered as potentially malignant and should be called choriocarcinoma, Grade I.

The comparative rarity of hydatid mole and extreme rarity of choriocarcinoma are also responsible in large part for the lack of early diagnosis. It is axiomatic that one never can make a diagnosis of any condition unless he has that condition in mind. The presence of hydatid mole is rarely suspected until the vesicles are passed, because the physician does not have the possibility of mole in mind when he sees a patient who is bleeding during her pregnancy. Very early hydatid moles also may be missed because of casual and incomplete examination of placental tissues by pathologists.

The possibility of choriocarcinoma is rarely suspected in a woman who bleeds after an abortion or a normal pregnancy because the attending physician does not have that condition in mind.

Hydropic degeneration can occur in the chorionic villi of any pregnancy and is responsible for many abortions. For this reason alone, every patient who has a miscarriage in the first trimester of pregnancy should have her uterus curetted, and the curettings should be examined microscopically so that the early abortion of a hydatid mole will not be overlooked, and a beginning choriocarcinoma exist unsuspected.

About 10 per cent of hydatid moles are followed by choriocarcinoma, according to most writers. Novak gives a figure of 1 to 2 per cent. The reason for this difference is due to the fact that many so-called chorionepitheliomas are not malignant. Hence, Novak's figures are more nearly correct. Every patient who

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passes a hydatid mole must be suspected of harboring a choriocarcinoma. After a woman has passed a mole, she should be curetted immediately. If there is bleeding after passage of a mole, the need for curettage is particularly important. The curettings should be examined for choriocarcinoma. Negative findings from curettage mean nothing, and the urine of the patient should be examined for chorionic gonadotrophic hormone by the Friedman test after ten days. Every two weeks thereafter, for two months, her urine should be subjected to a Friedman test. After this seventy days has passed, an examination of the urine should be made each month until a year has intervened since the passing of the mole. It goes without saying that any positive report must be confirmed and a new pregnancy ruled out. Only by this procedure can early diagnosis of postmolar choriocarcinoma be made.

Hydatid mole and choriocarcinoma are associated in the minds of many physicians to such an extent that they cannot think of one without the other. Many believe choriocarcinoma to follow hydatid mole in a much greater percentage of cases than it does, and have the mistaken idea that choriocarcinoma is such a common sequel to hydatid mole that they perform routine hysterectomies whenever the diagnosis of hydatid mole is made. Many never suspect the presence of choriocarcinoma unless there has been a preceding hydatid mole.

One obvious fact that seems to be little known is that any pregnancy, terminating early or at term, can be associated with or followed by choriocarcinoma. In our study, we found that more of the fatal choriocarcinomas followed abortions or full-term pregnancy than followed hydatid mole. One reason for the increase in mortality in these cases was that much more time elapsed before a diagnosis of choriocarcinoma as made than when the malignancy followed hydatid mole.

The primary, the most frequent, and the cardinal symptom of both hydatid mole and choriocarcinoma is bleeding. Any bleeding during pregnancy or other signs of threatened miscarriage must cause the thought of hydatid mole to be borne in mind. Likewise, any bleeding following miscarriage or pregnancy must also cause choriocarcinoma to be suspected.

When bleeding occurs during pregnancy, obviously the preliminary diagnosis of hydatid mole or of choriocarcinoma will be correct only a very few times and can only be an inferential one at best. The fear that manipulation might cause miscarriage should not prevent examination with a speculum. Vesicles in the vagina or carcinoma of the cervix might otherwise be overlooked. Quantitative Friedman tests are an added refinement in diagnosis, but in many localities cannot be performed because of the lack of trained technicians. The expense, too, of quantitative tests makes them prohibitive in all but the exceptional instance. It has been shown that normal pregnancies have a sudden high peak of urinary hormone one month after the first missed period. An increasing chorionic hormone content of the urine after this time, or one that does not decrease is very indicative of the presence of a hydatid mole or choriocarcinoma. Vesicles passed from the vagina verify the diagnosis of hydatid mole.

Too much importance has been attached to excessive enlargement of the uterus in the diagnosis of hydatid mole. In our study, the majority of patients with mole did not have a uterus enlarged beyond the period of pregnancy. We

agree with Mathieu in his condemnation of hysterotomy in the diagnosis of and curettage in the treatment of choriocarcinoma. In postmolar cases with positive Friedman tests and without bleeding, curettage is unnecessary for diagnosis and should give way to immediate hysterectomy. We found that, in fifty-five cases with positive Friedman tests, curettings agreed in only twenty-four. This is a serious indictment against curettage as a diagnostic procedure.

In one of our own cases and several found in our study, the original choriocarcinomas were several millimeters under the endometria, in the bodies of the uteri, and curettage could not have reached them. Hysterectomies were done because of persistently positive pregnancy tests following the passage of moles, and the patients' lives were saved as a result. However, in patients with postmolar bleeding, postabortal bleeding, or postpartum bleeding, curettage with examination of the curettings might be a valuable diagnostic aid. It can be done while awaiting the result of a Friedman test, and might be the means of saving valuable time in making a diagnosis because, if frozen sections should reveal choriocarcinoma to be present, an immediate hysterectomy could be done to great advantage.

Negative findings from curettage mean nothing. There is a real danger of uterine perforation with alarming hemorrhage in instances where the choriocarcinoma is of any extent. Seven cases were found, in our study, where the uterus had been perforated by the curette in the presence of choriocarcinoma; four of these patients died of resulting hemorrhage.

The ultimate clinical diagnostic method for choriocarcinoma is the biologic pregnancy test and, if this test is positive two weeks following pregnancy or the passage of a mole, hysterectomy should be performed. This dictum, however, has one exception. In those cases of hydatid mole which are associated with large lutein cysts of the ovary, it is possible to have a persistently positive pregnancy test due to the excretion of the gonadotrophic hormone which has been retained in the ovarian cysts. Some writers say that the pregnancy test is positive for six weeks after the passage of some moles. In the absence of palpable lutein cysts, we feel two weeks is the limit of safety.

Mathieu has said: "Just as in acute appendicitis and ectopic pregnancy, all patients (with chorionepithelioma) should be operated upon as soon as the diagnosis is made in order to obtain the best results and serve the common good. In a few cases in the literature it appeared that the uterus had been removed needlessly, but these cases are rarities and need have no effect in controlling our conduct. Surgeons who attach too much importance to the loss of the uterus are likely to neglect the common good. While there is occasionally an argument from a pathologist that certain lesions of chorionepithelioma might have regressed and thereby hysterectomy have been prevented, I do not believe that we should let the occasional negative pregnancy test or the occasional instance of regression, both of which are rarities, dominate the situation. I am sure that waiting for regression of the chorionepitheliomatous lesion does not constitute one of the factors responsible for the lowered mortality rate obtained at the present time. In this study of the literature, it was almost invariably found to be true that when the disease was diagnosed early and hysterectomy performed immediately, the patient was cured; and that, on the other hand, the deaths were recorded almost invariably among the cases in which there was either delay in diagnosis and treatment or in which the disease was of long standing."

Hysterectomy may be either total or subtotal, depending upon involvement of the cervix by the choriocarcinoma. If the cervix is not involved by the growth, it does not need to be removed.

X-ray of the lungs should always precede hysterectomy for choriocarcinoma because pulmonary metastases are frequently present before they are suspected and, if recognized early, may be treated by x-ray. Chorionatous tissue is particularly susceptible to x-ray. It has been stated that frequently metastases would disappear spontaneously after the parent tumor was removed. We found no evidence of this in our study and do not believe it.

The ovaries should be removed only when involved by the primary growth, or by metastases, or when the lutein cysts are so large that they are mechanically objectionable. In such an instance, the patient's age would be the deciding factor as to whether large lutein cysts should be removed. After the removal of the tumor which stimulated the lutein cysts, they will regress. When large lutein cysts of the ovaries are found, the presence of a trophoblastic tumor must be suspected. It is to be remembered that choriocarcinoma metastasizes through the blood stream and by direct extension. As a result of this method of extension, the ovaries are rarely involved in the growth, and a young woman in the childbearing age should not be castrated needlessly merely because her uterus happens to be the site of a choriocarcinoma. As far as we have been able to determine by study and from the literature, ovarian hormones play no part in the life of choriocarcinoma metastases.

The vagina and vulva should be examined carefully before hysterectomy because metastases to the vagina frequently occur very early and, in several cases in our study, vaginal metastases were the first sign of choriocarcinoma.

Mathieu stated, in his review of the literature, that early diagnosis of choriocarcinoma followed by hysterectomy was responsible for 95 per cent recovery in patients with choriocarcinoma. Novak takes exception to this statement.

The word, early, must be defined. Trophoblastic tissue is normally rapidly growing and invasive. Malignant trophoblastic tissue such as choriocarcinoma is particularly rapidly growing and invasive. Hence, what would be early treatment for ordinary carcinoma would not be for choriocarcinoma.

One hundred seven cases were reported to us classified under one or another of the terms mentioned earlier.

We arbitrarily set four months after the beginning of symptoms as the dividing line between early and late treatment. Where choriocarcinoma followed mole, the symptoms were considered to have started with the initial bleeding or with the passage of vesicles, whichever occurred first.

Where choriocarcinoma followed abortion, or full-term pregnancy, the symptoms were considered to have started either with the original bleeding or with the passage of the product of conception, whichever occurred first.

In the sixty-seven cases following mole, the mortality was roughly 15 per cent in both the early and the late group. In the forty cases following abortion or full-term pregnancy, the mortality in both groups was roughly 40 per cent. There were not enough cases, either after mole or otherwise, treated within two

months or earlier to give dependable figures; but that is the time that hysterectomy must be performed if the patient is to be given the best chance for life.

We feel that a distinction should be made between early diagnosis following the first symptom and early diagnosis following the inception of the tumor. In those cases where the choriocarcinoma started from a nidus deep in the uterine musculature, one can see that it could be a number of months after the choriocarcinoma started before the endometrium was encroached upon and bleeding resulted. Therefore, in such an instance, the diagnosis could have been made early following the first symptoms, but would have been late after the beginning of the tumor, and metastases might already have been present. Hysterectomy, in such an instance, cannot be expected to cure the patient. However, if such a patient had had the benefit of Friedman tests early, choriocarcinoma would have been suspected early; the uterus would have been removed while the growth was still localized; and the patient's life saved.

Early diagnosis means early diagnosis after inception of the tumor, not after the first symptom. In one of the cases encountered in our fifteen-year study, the patient had her first symptom thirty days after a full-term pregnancy. Biologic pregnancy tests were performed and verified and a hysterectomy was done immediately. The patient succumbed to pulmonary metastases. In retrospect, it is easy to see that this choriocarcinoma started early in the woman's pregnancy and was far advanced by the time the child was born. This was a case of early diagnosis after the first symptom, but late diagnosis following origin of the tumor.

Novak has justifiably criticized the figures in the studies published by Mathieu and Holman. He contends that some of the cases reported to us in answer to our questionnaires were not choriocarcinomas, and hence that the mortality figures are not correct. He is right. We have had to take the diagnosis of various pathologists for our reports. Some of these pathologists have had little or no experience with proved choriocarcinoma.

We hope that the Albert Mathieu Memorial Chorionepithelioma Registry, initiated by the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, will stimulate interest in the subject of choriocarcinoma.

If pathologists and clinicians will send tissues and histories of all suspected cases of choriocarcinoma to the registry, a valuable museum will be created. Increased experience will be gained in the study of choriocarcinoma. That experience will be reflected in better and more accurate figures concerning diagnosis and treatment of this most malignant tumor.

Summary

Confusion exists in the minds of many physicians as to the relation between hydatid mole and chorionepithelioma, due, in part, to vague and misleading pathologic classification. Classification of chorionepithelioma should be clarified, the word chorionepithelioma discarded and choriocarcinoma, Grades I to IV, used to replace it. Negative findings from curettage do not mean absence of choriocarcinoma. The biologic pregnancy test is the most valuable diagnostic aid. Choriocarcinoma following pregnancy or abortion is more often fatal than when following hydatid mole. Early hysterectomy is the best treatment for

choriocarcinoma; the type of operation having no effect on the mortality rate. Oophorectomy is unnecessary unless the ovaries are involved by the growth. The newly established Chorionepithelioma Registry will help in the study of this tumor and, in time, should contribute toward earlier diagnosis.

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Discussion

DR. EMIL NOVAK, Baltimore, Md.—Dr. Holman's late lamented Chief and colleague, Dr. Mathieu, was for many years deeply interested in this subject of chorionepithelioma, and made very valuable contributions to the subject. It was Dr. Holman's very generous gift to the Association which has made possible the Mathieu Registry, and I heartily endorse the plea he has made to you for your further cooperation in the work of this Registry.

With almost all of the statements made I fully agree. In the distinction between these benign and malignant trophoblastic growths we should always remember that even the trophoblast of a normal pregnancy possesses many of the characteristics which we associate with malignancy. When the egg makes contact with the uterus, its touch is the kiss of death, so to speak. It destroys the epithelium and the underlying tissue and it is this which permits the trophoblast to be invaded. It continues to grow and to destroy, penetrating the blood vessels and setting free the blood which is to fill the intervillous spaces. A physiologic form of metastasis even occurs, so that trophoblast and even clumps of villi are broken off in the vessels and transported to the lungs.

Pathologists should have no difficulty in differentiating between a frankly benign mole and a frankly malignant chorionepithelioma. However, there is a form of hydatidiform mole which penetrates the blood vessels deeply, often extending through to the peritoneum and sometimes causing serious or fatal intra-abdominal hemorrhage. And yet a mole of this type may not differ histologically from one of the usual benign type, in which the penetrating tendency is far more restrained. In other moles, without such extreme vascular penetration, the trophoblastic proliferation may be so marked as to make the pathologist suspect chorionepithelioma.

It is to this intermediate group that there have been applied such designations as "malignant mole" or chorioadenoma destruens. The latter term, suggested by Ewing, has always seemed to me to be a very poor one, although it is widely employed.

There is one factor, histologically intangible, which should never be lost sight of in the evaluation of this group of lesions. I refer to the defensive mechanism of the maternal tissues, commonly attributed to the decidua, though we know nothing as to its nature. It is this which holds the encroachment of trophoblast in check in normal pregnancy, and it is probably a countercharge of this defensive force which may even throw off a chorionepithelioma, a good many such instances of spontaneous regression having been reported.

In the diagnosis of this group of lesions, the microscope is the final arbiter, and no case of chorionepithelioma can be diagnosed on the basis of biologic tests alone. It was on

this point that I took issue with the conclusions of Mathien and Holman, in their publication of some years ago. Since this study did not include any microscopic investigation, I did not see any valid basis for the diagnosis of chorionepithelioma in most of their large series of cases. Nor can biological tests of any sort in themselves distinguish between a hydatidiform mole and a chorionepithelioma.

If, after the apparently thorough evacuation of a mole, the hormone titer remains high, perhaps for a good many months, a hysterectomy is indicated, but the removed uterus will in most cases not reveal a chorionepithelioma, though of course it occasionally may. Much more frequently, in my experience, it will show residual hydatidiform villi, often with marked trophoblastic proliferation, deep in the maternal vessels, where they are inaccessible to the curette, but keep up the production of large amounts of the chorionic hormone. It appears, therefore, that a good many hysterectomies must be done, and justifiably, for benign lesions to make sure that no case of malignant chorionepithelioma is missed. While residual molar tissue of this deeply lying type would probably regress, there is a definite chance that it may later give rise to an intramural chorionepithelioma, and this is further justification for the hysterectomy.

Finally, I have seen many cases of normal pregnancy in which chorionepithelioma had been diagnosed, because of extensive trophoblastic infiltration of both decidua and muscle wall, though large numbers of such infiltrating cells are often seen in the most normal pregnancy. After delivery, many of these cells, chiefly syncytial, may remain, often giving rise to "syncytial endometritis," which is not a neoplasm at all.

Finally, I wish to endorse Dr. Holman's plea for cooperation by the Fellows of this Society in the work of the Chorionepithelioma Registry.

DR. BERNARD J. HANLEY, Los Angeles, Calif.—Dr. Holman asked me to review our cases of chorionepithelioma at the Los Angeles County Hospital for the past fifteen years. The following is a summary:

We had had twenty-four cases diagnosed as chorionepithelioma; of these eleven are known dead, of whom ten were autopsied at the hospital and the diagnosis proved. One other patient died on the operating table from a spontaneous rupture of the uterus. Of the thirteen remaining patients that were alive, it is probable that one is now dead, inasmuch as she had metastatic nodules in the lungs and her Friedman test was positive when last seen. In a review of the microscopic sections still available nine had a syncytial invasion of the myometrium. These cases are probably not malignant and should not be classified as chorionepithelioma unless the malignancy be graded as Dr. Holman has suggested. If these nine cases are eliminated from our series it leaves fifteen cases of proved chorionepithelioma, of whom twelve are dead, a mortality of 75 per cent, which is about what one would expect in handling this highly malignant condition.

DR. FREDERICK H. FALLS, Chicago, Ill.—Dr. Novak's remark that the defense against this tumor is local may remind one of the work of Abderhalden and his test for pregnancy which depends upon the presence in the blood stream of an increase of the proteolytic ferments. When it was decided that this increase could be used as a test for pregnancy, he was not correct in thinking that the proteolytic ferments were specific, although they were responsible for the disintegration and the destruction of these so-called benign metastatic bits of placental villi which got into the circulation and are so frequently found in the lungs of normal women after delivery. I believe that this mechanism is part of the defense against chorionepithelioma; that if we knew how to increase this proteolytic ferment content of the blood we would then be able to combat this disease, even after the tumor cells have gone through the uterus.

I also would like to record a case we had in Chicago a few years ago—a woman about four months pregnant who had a hydatidiform mole and in whom the uterus was emptied by abdominal hysterotomy. At operation it was found that there was a chorionepithelioma which had already penetrated the uterus and involved the broad ligament.

INFLUENCES OF POSTURE ON THE URINARY TRACT IN PREGNANCY

JOHN PARKS, M.D., AND MICHAEL A. PUZAK, M.D., WASHINGTON, D. C.

(From the Departments of Obstetrics and Gynecology, George Washington University School of Medicine and Gallinger Municipal Hospital and the Department of Urology, Gallinger Municipal Hospital)

BASED upon the clinical observation that many patients received rather prompt relief from pyeloureteral pain by having the foot of the bed elevated about 15 degrees, it seemed worth while to investigate the possible influences of posture on the urinary tract in pregnancy. Adequate antibacterial agents, particularly the sulfonamides, have greatly reduced the morbidity and mortality due to pyelonephritis. However, the anatomic, physiologic, and mechanical factors which predispose the pregnant patient to urinary infections have not been changed by medications. These factors continue to deserve consideration in prevention, as well as in correction, of urinary disease.

Beginning in 1941, elevation of the foot of the bed became a part of the treatment of practically all prepartum patients admitted to Gallinger Municipal Hospital with symptoms and signs of pyelonephritis. During the five-year period from 1941 through 1946, 113 patients were treated for upper urinary tract infections complicating pregnancy. Ninety-six patients had prepartum urinary infections, and seventeen first developed symptoms in the postpartum period. This complication was present in less than 1 per cent of the 17,426 patients admitted to the Obstetric Division.

Pregnancy has been found to produce certain physiologic and pathologic changes in the urinary tract. Placental and growth hormones associated with pregnancy cause bilateral hypertrophy and hypoperistalsis of all musculofascial structures of the urinary system.¹⁻⁹ Some gestational factor, either anatomic or mechanical, usually brings about more dilatation of the right than of the left ureter.^{10, 11} The abdominal portion of the ureter undergoes the greatest amount of dilatation and tortuosity, whereas the most hypertrophy of the ureteral wall is demonstrable in that portion adjacent to and penetrating the bladder.^{3, 12-14} Practically all authors recognize stasis as a predisposing element to infection of the urinary tract in pregnancy. In addition, it is an interesting observation that bipeds develop more urinary tract problems in pregnancy than other mammals,¹⁵ and that pyelitis in the female occurs most frequently in childhood or during the period of gestation.¹⁶

Possible Postural Influences

As a plan for evaluating the importance of posture on the urinary tract in pregnancy, the following questions formed an outline for the present study:

1. Do changes in posture alter the position of the kidneys or change the contour of the abdominal ureters in pregnancy?

Read at the Fifty-Eighth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

2. Does fetal position have any influence on ureteral dilatation?
3. What changes occur in the pelvic portion of the ureter as a result of changes in position?
4. Does posture contribute to the predominance of right-sided dilatation?
5. What anatomic relations of the ureters influence their physiologic and pathologic changes?
6. Does the gravid uterus cause a shift in body fluids which in any way alters urinary excretion?

Procedure

Serial pyeloureterograms, taken with the patient in various positions, seemed the best means of demonstrating the influences of posture on the urinary tract in pregnancy. Certain limitations in pyeloureterography have always been present. Roentgen visualization of the bladder, kidney pelves, and abdominal ureters is easily accomplished either by intravenous or retrograde pyelography. It is much more difficult to demonstrate the contour of the pelvic portion of the ureters in pregnancy.

In an attempt to visualize the entire urinary tract, particularly the pelvic part of the ureters, consideration was given to the use of bulb-retention ureteral catheters which would permit filling the full length of the ureters. Such catheters have been devised by Kreutzman,¹⁷ but in recent years they have not been available. In order to produce as little distortion as possible of the pelvic ureters, the next best method seemed to be the insertion of soft number four catheters to a level with the pelvic brim. With the catheters in place, and following the injection of 20 c.c. of skiodan, pyeloureterograms were taken of each patient in the following positions: (1) supine; (2) with 15 degree elevation of the foot of the table; (3) with 15 degree elevation of the head of the table; (4) in the right oblique; and (5) in the left oblique position. Twenty-four patients who had recovered from the acute symptoms of pyelonephritis of pregnancy were studied in this manner. Each patient was placed on the cystoscopic table, in lithotomy position, with focus of the perpendicularly fixed roentgen tube as nearly as possible on the same area to prevent distortion of anatomic landmarks. As a rule, only the suprapelvic portion of the ureters and the bladder filled with the contrast media. The course of the pelvic ureters had to be determined by visualization of the small, indwelling ureteral catheters. From these pyeloureterograms, evaluation was made of the amount of upward and downward displacement of the kidneys and ureters brought about by changes in posture.

The next part of the study was carried out on another group of six patients who were known to have pyelonephritis in late pregnancy. With the foot of the table elevated 15 degrees, the kidney pelves and ureters were filled by retrograde injection with 20 c.c. of skiodan bilaterally. The catheters were immediately withdrawn and serial pyeloureterograms were made at five-, fifteen-, thirty-, and sixty-minute intervals. Four days later, the same patient received a similar retrograde injection of skiodan with the head of the table elevated 15 degrees, and comparable exposures were made. The beginning posture was alternated with every other patient. In this manner, the influence of posture on the dilation and emptying time of the dilated kidney pelves and ureters was determined.

A third method of examination was focused on the course of the pelvic ureters. Oblique exposures had failed to give as much information as desired about the ureter below the pelvic brim. In an attempt to determine what influence position might have upon anterior-posterior rotation, as well as upon upward and downward displacement of the ureters, stereoscopic roentgenograms were made with the patient standing and in 15 degree Trendelenburg position.

Findings demonstrated by the five patients who have thus far been examined stereoscopically will serve as a preliminary report on ureteral rotation.

While it has been impossible by present methods of investigation to evaluate changes in the caliber of the pelvic ureters, certain changes in position of the ureters with changes in posture have been demonstrated. The theoretical influence of these changes in ureteral position will be discussed under separate subject headings.

Mobility of the Kidneys and Abdominal Ureters

The findings of Woodruff and Milbert¹¹ and the x-ray evidence in this study indicate that kidney mobility is not influenced greatly by pregnancy. If altered at all, the kidneys are supported by the gravid uterus and are less mobile than in the nonpregnant patient. The degree of ureterectasis between the pelvic brim and the kidney pelvis does not change with alterations in position. It seems that posture has no direct influence on the position of the kidneys or upon the contour of the abdominal portion of the ureters in pregnancy.

Fetal Position and Ureteral Dilatation

With regard to fetal position in relation to ureteral dilatation, our findings are in accord with those of Hundley.³ Unequal ureteral dilatation, with greatest distortion usually on the right side, has been found with the occiput on either side of the pelvis and with breech presentations. These findings suggest that weight, contour, and position of the uterus are more significant factors in ureteral dilatation than is any intrauterine attitude of the fetus.

Postural Influences on the Pelvic Ureter

Comparison has been made between roentgenograms taken of the catheter-containing lower ureters with the foot of the table elevated 15 degrees and with the head of the table elevated 15 degrees. The terminal pelvic portion of the ureters and the presenting fetal part were consistently higher in the pelvis with the foot elevated than they were with the head of the table elevated. This amount of mobility is illustrated in Fig. 1. Movement of the lower uterine segment and adjacent ureters suggests that urinary function may be influenced by variations in position which produce stretch or release tension on the pelvic segment of the ureter.

Unequal Ureteral Dilatation in Pregnancy

One major unsolved problem in the study of pyelo-ureteritis is why symptomatic dilatation, stasis, and infection occur more frequently on the right than the left side. The theories advanced for greater dilatation of the right ureter have been dextrorotation of the uterus, the splinting influence of the sigmoid on the left, the angle of anatomic crossing of the ureter over the right iliac artery, and compression of the ureter at the pelvic brim on the right side. In Robertson's¹⁴ comprehensive review of 943 articles covering almost two centuries of literature on "Hydronephrosis and Pyelitis of Pregnancy," the theory of ureteral compression at the pelvic brim has a large number of advocates. It is primarily on the basis of the compression theory that postural procedures such as the knee-chest position, lying on the unaffected side, elevation of the foot of the bed, and resting on the face have been recommended as therapeutic measures.¹⁹⁻²² DeLee²³ doubted that compression caused ureteral dilatation. He advanced the thought of Luchs that the uterus, being about the same specific gravity as the other abdominal viscera, would not cause compression of the

ureter. Baird²⁴ has expressed the belief that gravity is more important in urinary drainage than is any release of pressure from Trendelenburg position. In line with the gravity theory, Fowler's position has long been advocated by clinicians as an important aid to postural drainage in pyelonephritis of pregnancy.^{25, 26} Other authors^{15, 27} have questioned the advantage of any postural maneuvers in the treatment of urinary tract infections in pregnancy.

While it is possible that the gravid uterus compresses and partially obstructs the ureter as it crosses the pelvic brim, this seems less likely than other considerations based on anatomic and x-ray findings. The ureter is fixed to the peritoneum and surrounding structures by fine fascial tissues which permit much greater lateral than longitudinal displacement. In its fascial attachments the ureter may be compared to a superficial vein. Longitudinal tension on a

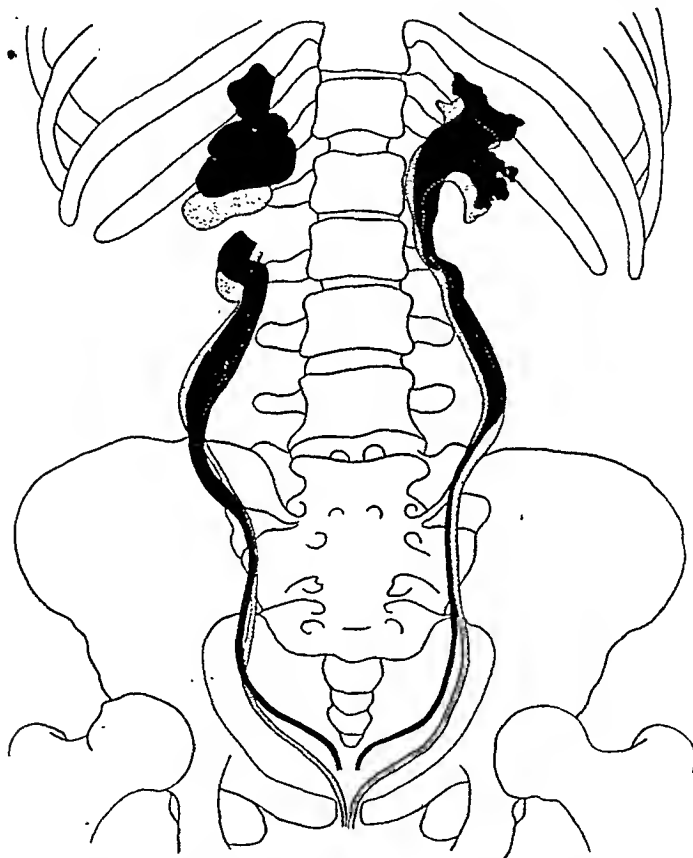


Fig. 1.—Drawing of superimposed pyeloureterograms. Position of the kidney pelves and ureters with the head of the table elevated 15 degrees is shown by the dotted outline. Upward movement of the ureters brought about by 15 degree elevation of the foot of the table is illustrated in black. The pelvic portion of the ureters shows a remarkable amount of mobility.

vein causes partial obliteration, whereas the vein can be carried laterally some distance before any degree of constriction occurs. As the ureters cross the iliac arteries and start their course down into the pelvis, they become surrounded by increasingly dense fascial sheaths. When the ureters reach a level with the ischial spines, they take an inward course to traverse the bases of the broad ligaments posterior to the uterine arteries, surrounded by the plexus of uterine veins (Curtis²⁸). This portion of the pelvic ureter becomes increased in the massive parametrial plexus of veins which make up the bulk of the cardinal or transverse cervical ligaments of Mackenrodt. Because of their intimate fixation to the juxtauterine portion of Mackenrodt's ligaments, changes in these important weight-bearing ligaments of the uterus will influence the course and

contour of the ureters. When the ligaments are carried downward, the ureters will be stretched in their longitudinal fascial sheaths and partially obliterated. When the weight of the uterus is shifted upward, the ureters will be carried upward with Mackenrodt's ligaments relieving stretch on the pelvic portion of the ureters. Thus far it has been impossible to demonstrate changes in the caliber of the pelvic ureter, but x-ray studies have shown that changes in position do cause on upward and downward movement of the terminal, intraligamentous parts of the ureters.

Preliminary stereoscopic x-ray studies of the lower ureters with small catheters in place and with the patient in an upright position have shown the right ureter to be more posterior than the left. When the foot of the table is elevated 15 degrees, the ureters tend to assume a similar anterior-posterior plane. One patient whose uterus showed no evidence of rotation or displacement was examined in the sixteenth week of pregnancy. In this instance the ureters remained in approximately the same anterior-posterior plane, but moved upward and downward with changes in position. Prather²⁹ has pointed out that uterine rotation with posterior displacement of the ovarian and uterine vessels may be a contributing influence to the predominance of changes in the right ureter. Additional investigation is needed to prove the correlation between uterine rotation and right ureteral dilatation.

Shift in Body Fluids in Pregnancy

By the sixteenth to the eighteenth week, the gravid uterus practically fills the true pelvis. All hollow structures passing through the pelvis are subjected to some pressure by the growing uterus.³⁰ Whether the pregnant woman stands, sits, or walks, the weight of the uterus causes congestion of the veins of the pelvis and lower extremities. Burwell³¹ has clearly demonstrated that venous pressure of the lower extremities rises by the fourth month and increases throughout the remaining course of pregnancy. Veal and Hussey³² have shown that pregnancy produces localized obstruction to the deep veins which impairs function of venous circulation in the lower extremities. Stagnation of blood in the lower extremities increases capillary pressure with a resultant loss of fluids from the circulation into the tissues. Theobald and Verney³³ found the only exception to this rule to be the patient with a pendulous abdomen in which the uterus does not fill the pelvis, but hangs forward suspended by the abdominal wall. When the pregnant patient assumes a recumbent position, fluids lost into the tissues by day return to the circulation to be excreted by the kidneys during the night. This contributes to nocturia, a rather common symptom in the last half of the prepartum period.

From serial pyeloureterograms, the majority of patients with dilated ureters showed more rapid dilution and elimination of the contrast media with 15 degree elevation of the foot of the table than with 15 or more degree elevation of the head of the cystoscopic table (Fig. 2). The immediate improvement in urinary elimination resulting from elevation of the foot of the table would seem to be due to release of ureteral tension by upward displacement of the uterus. If there is an associated edema of the lower extremities, release of pressure on the ilio-femoral veins will increase the urinary volume output.

From these findings, it follows that physiologic urinary stasis may be prevented by a liberal fluid intake and periods of bed rest, preferably with elevation of the hips and lower extremities, during the day as well as at night. Without stasis urinary tract infections are much less likely to occur in pregnancy.

Summary and Conclusions

The placental and growth-producing pituitary hormones cause bilateral hypertrophy of the urinary tract in proportion to the normal amount of muscu-



Fig. 2.—Serial pyeloureterograms showing more rapid dilution and elimination of skiodan from the impaired upper urinary tract with the patient in 15 degree Trendelenburg position as compared with 15 degree elevation of the head of the table. The presenting part is highest in the Trendelenburg position.

lofascial tissues in the system. The thinner abdominal portion of the ureter shows the greatest amount of dilatation and tortuosity in pregnancy. That part of the ureter which traverses the base of the broad ligament and enters the bladder wall is the thickest segment of the ureter both in the pregnant and in the nonpregnant patient. Periureteral fascial fixation increases as the ureter crosses the pelvic brim and approaches the bladder.

Until a method of investigation can be devised which permits complete visualization of the urinary tract without mechanical irritation or instrumentation, knowledge of the effect of pregnancy on urinary function will remain incomplete. However, interpretation of the pyelouterograms taken in this study seems to indicate that posture influences the urinary tract in pregnancy in the following manner:

1. There is no remarkable change in the position of the kidneys or in the contour of the abdominal ureters with changes in posture.

2. The pelvic portions of the ureters which pass through the base of the broad ligaments are carried upward and downward with changes in position of the gravid uterus.

3. In an upright position and with good abdominal support, many uteri rotate to the right. This occurs irrespective of the position of the fetus. When the uterus rotates, the transligamentous portion of the ureter is carried along with the large uterine vessels and Maackenrodt's ligaments. Whether or not greater stretch, torsion, and reduction in the lumen of the right ureter result from the dorsal and downward displacement brought about by dextrorotation has not been demonstrated. This is a possible explanation for the greater degree of dilatation usually present in the right ureter.

4. Contrast medium in the kidney pelves and ureters becomes diluted and is eliminated more rapidly when the weight of the uterus is displaced upward by 15 degree elevation of the foot of the bed than it does with the patient in an upright position.

5. A generous fluid intake plus rest in bed for 20 to 45 minutes once or twice during the day, preferably with the hips at a level higher than the shoulders, will avoid prolonged urinary stasis and help prevent infection.

6. Pregnant patients with costovertebral pain due to spasm and dilatation of partially obstructed ureters receive relief from elevation of the foot of the bed. The exact mechanism which produces this relief is not known, but the theory is advanced that upward displacement of the gravid uterus releases tension and torsion of the pelvic portion of the ureter, thereby removing spasm and partial obstruction to urinary flow.

The authors wish to express their sincere thanks to Dr. William P. Herbst, Head of the Department of Urology; to Drs. Gordon McDonald and Patrick Mullins, Residents in Urology; to Leslie Majors, X-ray Technician in the Department of Urology; and to the Obstetric Staff at Gallinger Hospital for their excellent cooperation in this study.

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Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—This is a fundamental piece of work which helps us to understand some of the anatomy of the ureter during pregnancy. This is particularly valuable because this anatomic knowledge is not available in works on anatomy. The average anatomist knows nothing about it because he does not see any anatomic material with the pregnant uterus in place.

When pregnancy occurs there is a physiologic inhibition of the activity of all smooth muscle which is under normal circumstances particularly noticeable in the genito-urinary tract. This is probably accounted for by the action of the corpus luteum hormone in the early months and similar acting placental hormone in the later months. Physiologically, this is necessary so far as the uterus is concerned to avoid abortion. It would seem that the quieting effect on the ureters, as shown by the decrease in the number of urethral peristalses per minute as observed by many writers prior to 1920, is a side-effect which may also be associated with dilatation of the upper portion of the ureter. The cause of the hypertrophy of the sheath of Waldeyer in the lower part of the ureter, as mentioned by Dr. Parks, probably is due to the stimulus to the muscle fibers of this structure by the same growth hormone that produces the hypertrophy of the uterine muscle fibers.

Raising the foot of the bed and turning the patient on the well side in cases of pyelitis has been practiced in our clinic for twenty-five years. There is no reasonable doubt about its favorable influence clinically.

Pyelitis of pregnancy so frequently mentioned in the literature is a misnomer. Dr. Parks was careful to use the term pyelonephritis which indicates correctly that the inflammatory reaction affects the parenchyma of the kidney. And the relief of tension in the ureter acts as would the opening of an abscess as far as preventing further absorption from the kidney tubules is concerned as far up as the cortex of the kidney.

I should like to ask Dr. Parks when this dilatation begins during pregnancy? Also, what is the explanation of the development of the condition of pyelonephritis in the puerperium?

as occurred in seventeen cases after the pressure of the pregnant uterus had been relieved, and the placental and ovarian hormones could no longer have been a factor in producing stasis?

The reason for the prevalence of pyelonephritis in girl babies has been ascribed to the presence of fecal material held against the short female urethra by the diaper. The colon bacillus group are by far the most common organisms found in such cases and one theory at least of pyelitis of pregnancy is that childhood infections never really completely clear up, a few organisms continuing to live in the urinary tract which when conditions of stasis occur during pregnancy light up the infection. It is my opinion from physical examination of patients in the puerperium that during this time postural changes would show mobility of the kidney which during the later months of pregnancy are not demonstrable.

I am wondering if Dr. Parks has made any observations as to the effect of the uterus arcuatus as opposed to the normal uterus in producing pressure phenomena on the ureter. These uteri are frequently unusually wide and deviate from the midline.

It would seem also that some other factor must be present as well as pressure from the uterus when we consider how infrequently one encounters pyelitis in large ovarian cysts and uterine fibroids, especially when either are of the intraligamentous variety.

I should like to call attention to a minor point in anatomy mentioned by Dr. Parks when he refers to the position of the ureter in relation to the uterine veins. It is my conception that the veins surround the artery and that the ureter is posterior to both. The exact course and position of these structures in the full-term pregnant woman are not known and are difficult to determine as indicated by the essayist. It is useless to look for this information where it ought to be found, in books on anatomy.

DR. ROBERT D. MUSSEY, Rochester, Minn.—It is refreshing to read a fundamental piece of work carried out in such a logical way. Clinical observation develops curiosity in the mind of the author, followed by a clinical method of investigation which in this instance entails the use of the ureterogram to test out his idea in regard to why the elevation of the foot of the bed has caused this relief; then the hypothesis that the reason this relief is obtained is because of the anatomy of the ureter in the pelvis and the pressure that is exerted by the pregnant uterus.

We are all familiar with the fact that the ureters in the majority of pregnant women are dilated. This has been demonstrated by a number of investigators. Also, it has been shown that the ureters remain dilated for a number of months after the birth of the child. It would be of interest, and perhaps Dr. Parks will follow this up, to have a series of ureterograms, much as Dr. Falls suggested, on some of the patients whom we are getting up so much earlier after confinement than we used to. There are those who feel it has been a mistake to get patients out of bed on the second or third day after confinement, and that we will rue this later on at the time of menopause or when operation becomes necessary to correct repairs caused perhaps by getting the patient out of bed too soon. It may be that a study of the ureters at this time would be of interest.

Up to the time of chemotherapy it was necessary to rely on certain measures such as rest in bed, forcing fluids, sedatives, and occasionally the employment of ureteral catheterization. I must confess that I have not been greatly impressed over a period of time by the posture of the patient in particular. We have relied chiefly on forcing fluids by the use of glucose intravenously, but I have become a convert and am perfectly willing to admit that the argument in regard to the elevation of the foot of the bed in these cases is a very good one. I would like to have further proof in regard to the reason why the right ureter is more dilated than the left.

DR. EDWARD L. CORNELL, Chicago, Ill.—When skiodan was first presented I had the opportunity at the Cook County Hospital of making a study of the ureter in pregnancy. It was interesting to observe practically the same findings that Dr. Parks has given us. It was also interesting to note that we found the ureter deformity in large fibroids of the uterus without pregnancy. In other words, it seemed to me that any tumefaction, whether it was pregnancy or fibroid or cyst of the ovary, gave the same findings.

It was also interesting at that time that we found the right ureter was markedly dilated over the left ureter in the vast majority of cases. It was seldom that the left ureter was dilated more than the right. I have a great deal of difficulty in convincing the urologist that stricture of the ureter is an important factor in many of these cases. I have difficulty with some of the obstetricians in convincing them that stricture of the ureter plays a part. Some of the urologists feel that stricture does play its part in dilatation of the ureter above the pelvic brim. I think Dr. Parks should bear that in mind when he continues his studies. The passage of a number five catheter does not always tell the true story. It is necessary to pass a number nine or larger dilator.

DR. PARKS (Closing).—We have not investigated urinary changes in the puerperium; 96 of the 113 patients reported in this study had pyelonephritis in the antepartum period.

Thus far we have not encountered a patient with pyelonephritis in association with an abnormal uterus or with levorotation of the uterus. It will be interesting to see if this theory holds in conditions which cause greater stretching and distortion of the left ureter. Anatomic fixation of the ureter is greatest in the terminal portion which is partially encircled by the large uterine veins.

Regarding the physical influence of large pelvic tumors, the ureter can stand a great deal of lateral displacement, but not a lot of longitudinal stretching. Theoretically, tumors which only displace the ureter laterally should not cause a great deal of urinary tract trouble.

HYSTERECTOMY*

A Study Based on 266 Personal Operations Performed in 1945 and 1946

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

(From the Carney Hospital)

THE literature of the last decade shows that an increasing number of gynecologists have adopted the total hysterectomy, or panhysterectomy, as the routine operation, and have reserved the supravaginal amputation of the uterus for special cases. This is a total reversal of the opinions held by gynecologists a quarter of a century ago. In 1932, at the forty-fifth annual meeting of this Association, I¹ presented a paper on hysterectomy, analyzing 554 hysterectomies performed on the Obstetrical and Gynecological Service of the Carney Hospital during a period of fifteen years; 300 of these operations having been performed by myself, and 254 by twelve other operators. This analysis showed that 40.0 per cent of these hysterectomies were total. In order to determine what changes have taken place in my practice since the presentation of that paper in 1932, I have analyzed these hysterectomies for the years 1945 and 1946, which form the basis of this paper.

In 1945 one hundred thirty-five operations were performed, and in 1946 one hundred thirty-one, a total of two hundred sixty-six hysterectomies during the two years. These were divided between abdominal and vaginal hysterectomies, 213 being abdominal and 53 vaginal procedures. In the group of 213 abdominal hysterectomies, 88.7 per cent were total; the remainder, or 11.3 per cent, were divided among cesarean hysterectomies, fundie hysterectomies, and supravaginal hysterectomies. In the group of 53 vaginal hysterectomies, 86.7 per cent were complete; the remainder, or 13.3 per cent, were divided between the composite operation (fundie hysterectomy, amputation of the cervix, and interposition of the middle portion of the uterus), 9.4 per cent, and vaginal supra-cervical hysterectomy, 3.9 per cent.

According to the above figures, I am now doing more than twice the number of panhysterectomies that I was doing fifteen years ago. At the present time the total operation is done routinely, and the subtotal operation is reserved for special reasons or indications. Under present-day conditions the mortality of panhysterectomy, in experienced hands, should not be greater than that of the less formidable procedure. The convalescence has been simplified by proper preoperative care so that the patient reaches the operating table in improved or satisfactory condition, and the postoperative care has been greatly improved through the intravenous administration of blood, blood plasma, amino acids, glucose, and physiologic saline solution. The sulfonamides and the antibiotics have played an important role in combatting infection, and the great improvement in anesthesia during the last two decades, early ambulation, and the present-day management of thrombophlebitis and phlebothrombosis should receive their full share of credit in this general improvement.

The technique of operation has not changed remarkably during the past fifteen years—one noteworthy point, however, has been the tendency toward

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closing the vagina and the abdomen without drainage. In the early days of the sulfonamides, sulfanilamide or sulfathiazole was left in the pelvis before the abdomen was closed, but, in a comparable series, with and without these remedial agents, it has been proved to my satisfaction that there is but little or no difference in the postoperative period. The improved results should be ascribed to better surgery in general, to the employment of finer sutures, and to better pre- and postoperative care, rather than to the use of the sulfonamides. Again, experience has shown that these substances exert their most satisfactory effect when given orally or parenterally.

In this group of 266 patients the ages were as follows: between 20 and 29 years, ten patients; between 30 and 39 years, sixty-three patients; between 40 and 49 years, one hundred twenty-five patients; between 50 and 59 years, forty-six patients; between 60 and 69 years, seventeen patients, and between 70 and 79 years, five patients.

Before their last admission to the hospital 158 previous operations had been performed on these patients—in other words, 59.7 per cent had been operated upon previously. In eighty-six the operations were of a gynecologic nature and consisted of the following: fundie hysterectomy, abdominal hysterotomy, myomectomy, cesarean section, ventral suspension of the uterus, round ligament suspension of the uterus, pelvic sympathectomy, salpingo-oophorectomy, oophorectomy, salpingectomy, amputation of the cervix, trachelorrhaphy, cauterization of the cervix, dilatation and curettage, biopsy of the cervix, radium implantation, colpoperineorrhaphy, Kennedy operation for incontinence of urine, vaginal plastic operations, hysterosalpingectomy, anterior colporrhaphy, resection of ovaries, and abdominal fixation of the uterus, with or without a previous plastic operation. In seventy-two the operations were of a non-gynecologic nature and consisted of: appendectomy, appendectomy during pregnancy, cholecystectomy, nephrectomy, operation for diverticulitis, inguinal herniorrhaphy, and thyroidectomy.

TABLE 1. PRINCIPAL DIAGNOSES

<i>Uterine pathology:</i>	<i>Cervix:</i>	Malignant	4
		Benign	11
	<i>Corpus:</i>	Malignant	6
		Benign	189
<i>Ovarian pathology:</i>		Malignant	2
		Benign	30
<i>Tubal pathology:</i>		Malignant	0
		Benign	16
<i>Miscellaneous:</i>			4

Four cesarean hysterectomies were performed; three for multiple myomas and one for hemorrhage associated with central placenta previa.

In addition to these 266 principal diagnoses, 392 supplementary diagnoses of a gynecologic, and 159 supplementary diagnoses of a nongynecologic nature were made. Space does not permit the separate listing of these supplementary diagnoses.

The indications for the seven Wertheim operations were as follows: Carcinoma of the cervix, three; carcinoma of cervical polyp and corpus carcinoma, one; endometrial sarcoma, one; pelvic endometriosis, severe, one; and multiple myomas with severe endometriosis of rectovaginal septum and right ovary, one.

In connection with the 266 principal operations listed above, 411 concomitant operations were performed, 260 being of a gynecologic nature, and 151 of a nongynecologic nature. The adnexa were removed completely in 139 patients, and partially in 34 patients, a total of 173 patients.

TABLE II. TYPES OF HYSTERECTOMIES PERFORMED

<i>Abdominal:</i>	Panhysterectomy	182	
	Wertheim	7	
	Supravaginal	18	
	Fundic	2	
<i>Vaginal:</i>	Cesarean hysterectomy	4	213
	Panhysterectomy	46	
	Supracervical, with interposition of cervical stump	2	
	Composite operation (fundic hysterectomy, amputation of cervix, and interposition of middle portion of uterus)	5	53
Total			266

General anesthesia was administered in 65 per cent of the patients, and spinal anesthesia in the remaining 35 per cent.

Drainage was instituted in thirty-two abdominal hysterectomies as follows: Wertheim operation, six patients; abdominal panhysterectomy, nineteen patients; supravaginal hysterectomy, three patients; cesarean hysterectomy, four patients, and vaginal hysterectomy, forty-five patients.

Sulfanilamide powder was left in the pelvis in 104 cases of abdominal hysterectomy and omitted in the remaining 109 cases.

Transfusions were given pre-, intra-, and postoperatively to 103 patients in this group; fifty were transfused with whole blood, and fifty-three with blood plasma. The largest amount given to any single person in the group was 2,000 c.c. which was given to a patient who had had an abdominal panhysterectomy, and the largest amount of blood plasma that was given was 2,000 c.c. to one who had had a supravaginal hysterectomy.

In addition to the abdominal hysterectomy, vaginal plastic operations were performed in sixty, or 22 per cent of the patients.

The postoperative complications were included in the group of 551 supplementary diagnoses, 392 of which were of a gynecologic nature, and 159 of a non-gynecologic nature. Space does not permit listing these in detail. It should be stated, however, that all complications were overcome under accepted and adequate management.

Mortality

Three women died in this group of 266, a gross mortality of 1.1 per cent. All three deaths occurred in 1945; there were no deaths in the 131 hysterectomies performed in 1946. The details of these deaths follow:

CASE 1.—Mrs. S. L., 47 years of age, was operated on because of a large myoma uteri, a scarred cervix, a first degree rectocele, and a relaxed perineum. The operation was performed on April 25, 1945, and consisted of a panhysterectomy, a bilateral salpingo-oophorectomy, and an incidental appendectomy. The patient had a perfectly normal postoperative course, and was discharged from the hospital on the fourteenth postoperative day. Examination that morning revealed an entirely satisfactory operative result, and there was no evidence of pathology of the venous system. On arriving home she experienced an attack of collapse, dyspnea, cyanosis, and rapid pulse. Her family doctor administered oxygen and sent her back to the hospital with a diagnosis of "Massive Pulmonary Embolism." She was pronounced dead at 12:20 p.m., about five minutes after readmission to the hospital. Her husband refused autopsy.

CASE 2.—Mrs. H. P., 45 years of age, had lysis of adhesions, a supravaginal hysterectomy, bilateral salpingo-oophorectomy, and an appendectomy with pelvic drainage on June 25, 1945, for a gangrenous, submucous myoma of the uterus.

gangrenous adnexa, bilateral tuboovarian abscesses, and periappendicitis. On July 4, 1945, two cigarette drains were removed. After a prolonged febrile course, during which time adequate sulfanilamide and penicillin therapy, together with two blood transfusions were given, the diagnosis of a lung abscess was made by x-ray on July 18, 1945. Following this there was extreme difficulty in breathing, and marked râles over both lungs. The pulse rate was slow and irregular, and the blood pressure was 112/70. Stimulants were given, but she expired at 8:50 P.M. Permission for an autopsy could not be obtained.

CASE 3.—Mrs. C. D., a primigravida, 42 years of age, was delivered by low transverse cervical cesarean section, under local anesthesia, because of a fifty-two hour labor and cephalopelvic disproportion. Three hours after operation the uterus relaxed and there was moderate postpartum hemorrhage. This condition responded to intravenous ergotrate, 500 c.c. of blood plasma, and 500 c.c. of whole blood. Subsequently she developed bronchopneumonia which was treated by the Medical Service. After recovering from the pneumonia she had two postpartum hemorrhages, the first was mild and was controlled by uterovaginal tamponade, the second, which occurred on April 22, 1945, was severe. Uterovaginal tamponade again controlled the hemorrhage and she was given another 500 c.c. of whole blood transfusion. The following day the packing was removed, there was no bleeding, but a large amount of creamy lochia escaped from the uterus. A piece of necrotic placenta, the size of a large grape, was removed from the fundus, the uterus was packed with sulfanilamide gauze, and she was returned to bed in good condition. Thus far 1,250 c.c. of blood plasma and 1,500 c.c. of whole blood had been administered.

On April 28, 1945, supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed. Five grams of sulfanilamide powder were placed in the cul-de-sac and the pelvis was drained through the vagina. On May 7, 1945, wound dehiscence occurred, with extrusion of the omentum through the incision. Under spinal anesthesia a portion of the omentum was resected and the incision closed. On May 10, 1945, she passed a large clot by vagina, and on May 12 she passed another large clot. Her condition was fair. Vaginal packing with sulfanilamide gauze controlled the hemorrhage. On May 13, 1945, there was no bleeding by vagina, and the packing was left in place. On May 14, 1945, at 7 A.M., there was slight bleeding, and at 10 A.M. a large clot was passed. During the afternoon an enormous clot was passed; it filled the bottom of a bedpan, and the patient went into shock. Three units of blood plasma were given intravenously, and the vagina was packed, but she did not respond to treatment and expired at 4:45 P.M. Permission for an autopsy could not be obtained.

Summary and Conclusions

1. Two hundred sixty-six hysterectomies performed by the author in 1945 and 1946 are reported.
2. In this group there were 213 abdominal hysterectomies, of which 88.7 per cent were total.
3. In fifty-three vaginal hysterectomies included in the series 86.7 per cent were total.
4. There were three deaths in the 266 patients, a gross mortality of 1.1 per cent. One death occurred after a panhysterectomy and two after supravaginal hysterectomies.
5. One hundred three patients, 38.7 per cent, were given transfusions; 53 patients, 51.4 per cent, were given blood plasma; and 50 patients, 48.5 per cent, whole blood.

6. I advocate panhysterectomy as the routine operation when the removal of the uterus becomes necessary, and reserve the subtotal operation for special indications.

7. In experienced hands, with the present-day preoperative and postoperative care, the mortality of panhysterectomy should not be higher than that of supravaginal hysterectomy.

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Discussion

DR. WILLIAM F. MENGERT, Dallas, Texas.—Dr. Phaneuf has ably presented an account of personal performance, with an over-all death rate of 1.1 per cent. He stressed the changing order regarding hysterectomy and pointed out that he is now doing the total operation routinely. He advocates panhysterectomy and states that in experienced hands, with present-day pre- and postoperative care, the mortality should not be higher than that of supravaginal hysterectomy. These statements deserve careful consideration.

Four years ago I reported before this Association the University of Iowa experience with 1,920 total abdominal hysterectomies. These were done by some fifteen or twenty operators, of which I was one, and there was but one death among the last 343 total hysterectomies in the series. More than half of these operations were performed by residents in training.

Since then I instituted routine total hysterectomy at Parkland Hospital in Dallas. Residents working alone or under direction have performed a total of 326 hysterectomies on the Obstetric and Gynecologic services, with but four deaths, 1.2 per cent. These deaths included hemorrhage from a ruptured pregnant uterus, a purely anesthetic death, uremia from lower nephron nephrosis following mismatched blood transfusion, and a postoperative peritonitis. There were 275 total abdominal hysterectomies, including five obstetric patients, with three deaths, 1.1 per cent. There were 270 elective panhysterectomies performed on the Gynecologic division with but two deaths, or 0.7 per cent. There was one cut ureter in this series.

We close the abdomen without drainage. I do not think any of those patients were drained abdominally. The wound bed is extraperitonized and drained vaginally for twelve to eighteen hours, routinely.

Total hysterectomy is necessary in the presence of endometrial, ovarian, or tubal malignancy. It is necessary for pelvic inflammatory disease and is desirable for myoma. Men like Dr. Phaneuf have brought forth a change in the old order. The advocate of total hysterectomy no longer needs to defend his position. On the contrary, there is rarely indication for incomplete operation when removal of the uterus is necessary. I think we should stress this point, because too many subtotal operations are performed too often by too many operators for no other reason than that the woman has a uterus. Hysterectomy for recognizable disease is for the experienced operator alone, and should be of the total variety.

DR. EDMUNDO G. MURRAY, Buenos Aires.—On the subject of total or subtotal hysterectomy I am of the same opinion as Dr. Phaneuf. The reasons are fourteen cases of cervical carcinoma I have recorded that appeared after subtotal hysterectomy. I have also observed pelvic postoperative infections, probably due to cervical inflammations. When the cervix is not removed with the uterus I always coagulate it with electrosurgery immediately after the subtotal hysterectomy.

The Argentine gynecologic clinics are enthusiasts on conservative surgery. I have done myself during the last ten years more conservative uterine operations than radical surgery. It is meant certainly for benign conditions.

I would like finally to call attention to a conservative surgical technique employed in fibromyoma of the uterus, and devised by Carlos R. Cirio of Buenos Aires. The first steps are those of a normal fundal hysterectomy. Once the fundus is open the procedure consists in removing with electrosurgery the myometrium of the anterior and the posterior wall of the uterus, with the nodules included in it. The internal wall remaining, formed by endometrium and a thin layer of musculature, is brought together at the fundus with interrupted sutures. The external wall is closed over the internal in the same way.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—I would like to mention one item that I think should be recorded by this Association. The late Dr. James E. King did not have a death following hysterectomy after May, 1934. For the past six years at the Buffalo General Hospital we have been employing the total operation routinely, somewhat to Dr. King's displeasure, because he always believed that for benign disease the subtotal operation was to be preferred. During that twelve plus years Dr. King performed over 850 consecutive hysterectomies without a death, leaving us quite a record to attempt to equal with the total operation.

DR. WILLIAM H. WEIR, Cleveland, Ohio.—I have been a proponent of total hysterectomy and have performed it in 100 per cent of my cases in the past thirty years. There is one point to be brought out, and that is the advisability of coincident perineal repair if it be necessary. Lately I have been having one case after another of prolapsing cervix developing after previous supravaginal hysterectomy by some other operator who failed to repair a relaxed vaginal outlet at the same time. Many of these cervixes have been markedly diseased and certainly should have been removed at the original operation. When the entire uterus had been removed but the repair had been neglected, the prolapsing structures offered a more difficult problem. The trouble is that many of these hysterectomies were performed by men who had no proper conception of gynecologic problems. They would perform a supravaginal hysterectomy, perhaps for a simple unoffending fibroid, and ignore the existence of a badly damaged cervix and relaxed perineal or vesical supports. It is usually much simpler to remove the cervix at the time of the hysterectomy than to remove it after a supravaginal hysterectomy.

In our clinic we have had a higher mortality with our supravaginal than with our panhysterectomies. This may be explained by the fact that in a very difficult case one is likely to leave the cervix to shorten the operation, and these difficult or badly infected cases naturally show a higher death rate.

DR. PHANEUF (Closing).—In answer to Dr. Mengert's question about drainage, I wish to state that, when indicated, we usually drain hysterectomies vaginally. We drain the pelvis in cases where the peritoneum is insufficient to cover all raw areas, a condition encountered in severe endometriosis and chronic pelvic inflammatory disease. Our custom is to introduce a small iodoform gauze drain through an opening left in the center of the vaginal cuff, the double end of the gauze goes into the vagina, and the free ends are spread over to the sides of the pelvis, the sigmoid is swung over to the right side and, by uniting it to the peritoneum of the right lateral pelvic wall, to the bladder peritoneum and to the peritoneum of the left lateral pelvic wall, the pelvis becomes roofed over by the sigmoid, and the raw areas under the sigmoid are drained through the vagina.

Dr. Mengert has mentioned having seen fourteen cases of carcinoma of the cervical stump, and this led him to the more frequent use of panhysterectomy. The first hysterectomy that I ever did was a panhysterectomy. My former chief, the late Dr. Frederick W. Johnson of Boston, was doing panhysterectomies exclusively in 1913, at a time when no one else was doing this operation for benign disease of the uterus in our section of the country. During the twenty-five years we were associated on the Carney Hospital Service I saw him do but one supravaginal hysterectomy, and that was on a spinster with a fundal myoma and a very long cervix. His reason for advocating panhysterectomy was that he also had seen a number of carcinomas of the cervical stump, which led him to the decision that supravaginal hysterectomy

tomy was not a good operation. As a matter of prophylaxis against stump carcinoma, we have an absolute method when we remove the entire uterus while operating for benign uterine disease.

Dr. Murray has mentioned his method of performing hysteromyomeectomy. I believe this method is a sound one when applied to the younger group of women.

Dr. Randall spoke of the record of Dr. James E. King of Buffalo, who performed 850 hysterectomies without a death. Obviously this is an amazing series and one hard to duplicate.

We know that for many years Dr. Weir has advocated the removal of the entire uterus while performing hysterectomy. The technique of his procedure is well illustrated in our Transactions for 1931. He has also stressed the advantage of perineal repair in connection with panhysterectomy. In the series of cases that we have presented we had done perineal work in 22 per cent. Our method of procedure is to do the panhysterectomy first, and, if at the end of this intervention the patient is in good condition, we do the perineorrhaphy immediately. If, on the other hand, it is observed that the hysterectomy is a sufficient operation for that day, we return the patient to bed and repair the pelvic floor, under local anesthesia, three to six months later, as a second-stage operation.

DIVERTICULITIS: SYMPTOMS, COMPLICATIONS, AND MANAGEMENT, PARTICULARLY IN THE FEMALE*

VIRGIL S. COUNSELLER, M.D., ROCHESTER, MINN.

(From the Division of Surgery, Mayo Clinic)

MUCH progress has been made in recent years in the diagnosis and management of diseases of the colon, especially by the roentgenologist, who can now accurately distinguish between inflammatory and malignant lesions. Another great aid has been the introduction of the sulfonamide drugs.

Diverticulitis is an inflammatory disease of diverticula of the colon. It now is easily recognizable, and is much more satisfactorily treated than before, both medically and surgically, with a very marked reduction in the operative mortality rate.

Incidence of Diverticula

The incidence of diverticula (diverticulosis) of the colon is not accurately known because all affected persons do not undergo roentgenologic examination of the colon, which is the only positive method of identifying the condition, except for direct inspection of the colon during other surgical procedures in the abdomen and at necropsy. Morton reported the incidence of diverticulosis to be 15 per cent in 8,500 necropsies, while Brown of the Mayo Clinic reported that diverticulosis was seen in 8.5 per cent of the patients examined roentgenologically and in 5 per cent of those who came to necropsy. As Brown also said, these figures must be considered in terms of age, for it is known that diverticula of the colon are rarely seen in persons less than 30 years old, that 4 per cent are encountered in persons between the ages of 30 and 40 years, and that approximately 95 per cent occur in persons 40 years of age or older.

Origin of Diverticula

The foregoing figures certainly indicate that these diverticula of the colon are acquired and not congenital. Why some individuals acquire them and others do not is unknown, but it can be reasonably supposed that some congenital defects of the musculature of the wall of the colon may affect, or have a part in, the development of these pouches.

Almost everyone is agreed as to the probable mechanism of production of diverticula; namely, that they result from the action of contractions occurring simultaneously distal and proximal to a normal segment of bowel. Increased tension which is created in a normal segment by this mechanism causes herniation of small portions of the mucosa through the wall of the bowel at areas of least resistance, which are most likely located where blood vessels pierce the wall of the bowel.

*Read at the Fifty-Eighth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

Production of Diverticulitis

Inflammation of these mucosal hernias, then, is designated as "diverticulitis." We know that diverticulitis will not develop in all people who have diverticulosis, but we do not know what proportion of patients with diverticulosis will have diverticulitis. However, Abell has estimated that 10 to 20 per cent, and Brown and Mareley that 12 to 16 per cent of patients with diverticulosis ultimately will have diverticulitis.

Type of Treatment

The next bit of information we should have is what per cent of those with diverticulitis can we reasonably expect to require only medical treatment and what per cent will require surgical treatment. In a recent surgical study of this disease, Pemberton, Black, and Maino reported that of 600 patients who had diverticulitis, 144, or 24 per cent, were treated surgically, so that from their experience they feel it could be said that in about one of every four patients with diverticulitis complications requiring surgical treatment will develop.

Distribution of Lesions

The distribution of diverticula of the colon is of considerable importance. About 80 per cent of the lesions are located in the sigmoid, and the remaining per cent are distributed in a decreasing proportion toward the cecum. Weber said that he practically never sees diverticulitis situated above the crest of the ileum in a roentgenogram of the colon. The sigmoid colon is in close proximity or adjacent to the female pelvic organs, so that diverticulitis of this segment of the bowel can and does extend to these other structures. Diverticulitis can involve the adnexa on either one side or both sides and occasionally the urinary bladder, but the latter has some protection from the sigmoid when the uterus is in its normal anterior position. The importance of the differential diagnosis of inherent lesions of the sigmoid and the female pelvic structures is immediately apparent.

Diagnosis

The symptoms are those related to some inflammatory process within the abdomen, and usually in the pelvis or low in the left lower abdominal quadrant. These are pain, increase in temperature, and leucocytosis. If the process is a recurring one, or one of several weeks' duration, there may be signs of obstruction, perforation, formation of abscess, and fistula, either enteric, vesical, or cutaneous. The symptoms depend on the severity of the inflammatory process and its progression. That is, the process may be confined to the diverticulum only, but in some instances a small abscess will form which perforates and extends along the wall of the bowel, producing a thickened, narrowed tubelike structure with partial or complete obstruction of the colon. If the abscess extends to the adnexa, the signs become those of a tubo-ovarian abscess or abscess of the cul-de-sac of Douglas.

Sigmoidoscopy frequently is of very distinct aid in establishment of the correct diagnosis, or at least, in giving such evidence as to cause the physician

to be strongly suspicious that diverticulitis was the basis of the difficulty. For example, Jackman and Buie reported five signs that indicate diverticulitis: (1) limited mobility of a segment of the bowel that normally is freely movable, (2) angulation of the upper part of the rectum because of inflammation, (3) reduced lumen and adherent mucosal folds, (4) sacculization of the sigmoid, and (5) actual visualization of the diverticula.

The roentgenologist is most helpful in determining the diagnosis by means of the barium enema. If the lumen of the colon is completely obstructed, then all the roentgenologist can state is that there is obstruction which may be inflammatory or malignant, but if the barium will pass through and above the lesion, a picture results which can be interpreted as characteristic of an inflammatory or malignant condition. In the former instance the mucosa is uninvolved; it presents a feathery appearance, and the lesion extends along the bowel, whereas in the latter case the mucosal pattern ceases abruptly and extends around the bowel, instead of along the long axis of the bowel. When a perforation has occurred and a perisigmoidal abscess supervenes, the barium may pass through the opening and outline the abscess. A sigmoidovesical fistula rarely can be demonstrated by a barium enema, but gas and feces which are expelled from the urethra after the development of some inflammatory process in the left side of the pelvis usually are attributed to diverticulitis.

When a female patient has a mass in the left adnexal region which may seem, on bimanual examination, to be situated a little higher than usual, a roentgenogram of the colon not infrequently is most helpful in differential diagnosis. A carcinoma of the colon without many symptoms referable to the bowel or tenderness may be mistaken for a solid tumor of the ovary. Such a situation I have experienced on a few occasions. The roentgenologist usually, as previously stated, can establish the diagnosis, but at surgical exploration it is quite impossible in some instances to determine grossly if the lesion is inflammatory or malignant. The two lesions have many features in common. A pelvic mass which has been diagnosed as "pelvic inflammatory disease" or "pelvic tumor" can very well be regarded with the suspicion that it is primarily diverticulitis. The following case is representative.

CASE 1.—A woman 53 years old came to the Mayo Clinic on Jan. 10, 1946, complaining of constipation. She said she had been perfectly well until Dec. 1, 1945, when she had become constipated. Constipation gradually had become worse during the next three weeks. Then she had begun to have some degree of fever. She had been hospitalized at home for awhile and had improved, but after being discharged she had become worse, so that it was necessary for her to re-enter the hospital. At this time a tumor mass had been found in the pelvis, and for this she had been referred to the clinic.

On examination she was seen to be rather obese and not acutely ill. The leucocyte count was 12,100, and the erythrocyte count, 4,960,000 cells per cubic millimeter of blood. The value for hemoglobin was 12.3 Gm. per 100 c.c. of blood. The sedimentation rate (Westergren) was 45 mm. in one hour. The blood pressure was 124/84, expressed in millimeters of mercury. The temperature was 99° F. (37.2° C.). On pelvic examination, a mass was found which was diagnosed as a large pelvic tumor, probably uterine, with some compression of the rectum. Pelvic exploration was advised and performed on Jan. 16, 1946, by Dr. Waugh.

A primary lower midline incision was made. The patient was found to have very active subacute perforating diverticulitis involving the lower two-thirds of the sigmoid. The adnexa were normal. The uterus contained only very small fibroids, which were of no consequence. Gallstones were noted. Extraperitoneal resection of the lower two-thirds of the sigmoid was performed, with removal of all of the involved bowel, and use of a three-bladed clamp. A colonic stoma was created, which was closed at a later date.

Acute pelvic inflammatory disease and acute diverticulitis easily may be confused clinically, and a serious diagnostic error may be made. When this possibility presents itself, a roentgenogram of the colon can be most useful. The following case is an excellent example.

CASE 2.—A woman 43 years old was admitted to St. Marys Hospital on the gynecologic service because of acute lower abdominal crampy pains which had lasted for ten hours. Pain was situated mostly in the left lower abdominal quadrant, and was increasing in intensity. The pain was nonextending, but it doubled the patient up and caused her to perspire. It became worse when she moved about. The pain gradually increased and then subsided. Nausea was moderate. There was no change in bowel habits. Menstrual periods were normal.

On examination the patient did not appear to be acutely ill. Intestinal peristalsis was normal, but there was acute tenderness over the entire left lower abdominal quadrant; this tenderness overlapped the midline. Rebound tenderness was noted. The blood pressure was 130/80. The pulse rate was 108 per minute. Emergency leucocyte count disclosed 13,000 cells per cubic millimeter of blood. The urine was normal. On vaginal examination a copious, creamy-white discharge was noted. There was considerable tenderness when the cervix and uterus were moved. A roentgenogram of the colon revealed diverticulitis which involved the sigmoid, with mild deformity and no obstruction. In about twenty-four hours an ill-defined mass could be distinguished in the left lower abdominal quadrant. With the patient under medical management the process subsided, and she was dismissed five days later.

Medical Management

This case also serves to remind us that under appropriate management, such instances of diverticulitis will subside in 75 per cent of cases, but may recur. Briefly, the nonsurgical management consists of absolute rest in bed until the infection has subsided. This period will vary from two to three weeks. The external application of heat has been found to be very beneficial; the best method of application is diathermy. The daily oral administration of 6 to 8 Gm. of sulfasuxidine, 15 minims (0.92 c.c.) of tincture of belladonna three times a day after meals, and a half-ounce (14.8 c.c.) of mineral oil twice a day, is about all the medication which is needed, except for mild sedative agents. A bland diet is always recommended.

Complications and the Management Thereof

The complications of diverticulitis are as stated, notably perforation, obstruction, and formation of fistulas, and it is patients who have this group of symptoms who require surgical treatment. It has been observed that those patients in whom these complications usually develop have a more severe and in-

tense illness from the onset, and they appear to be more sick than the patients who will not require surgical treatment. The process does not subside under appropriate treatment, but when it does show some regression, the inflammation seems to continue, as a result, usually, of perforation into the bladder, adjacent loop of small bowel or through the abdominal wall, or of the formation of tubo-ovarian abscess.

A sigmoidovesical fistula is one complication, however, which can develop rather insidiously as well as rapidly. The symptoms are primarily vesical, with a considerable degree of dysuria, pyuria, and the passage of particles of feces and of gas through the urethra. Such fistulas never heal spontaneously, as do some cutaneous fistulas from the sigmoid. The following case is a good example of sigmoidovesical fistula.

CASE 3.—A woman 58 years old first came to the clinic in June, 1943, for exophthalmic goiter. She returned in April, 1946, for recurrent exophthalmic goiter. At her last visit she related that she had experienced some lower abdominal discomfort periodically, but that it was not very severe. She mentioned it because symptoms referable to the urinary system had developed. She also said that she passed some gas through the urethra. Cystoscopic examination disclosed only some cystitis. Pyuria of grade 2 to 3 was present. A roentgenogram of the colon revealed diverticulitis, with perforation and a sigmoidovesical fistula. Operation was advised.

At operation by Dr. Pemberton on June 17, 1946, a primary lower left rectus incision was made. The sigmoid was found to be adherent to the bladder on the right side near the dome, just to the right of the midline. The bowel was easily separated from the bladder. The fistulous tract was about 1 cm. in diameter. The opening in the bladder was closed with chromic catgut sutures and the segment of sigmoid which contained the diverticulis was brought out as an extrafascial exteriorization operation. Eleven days later, on June 28, 1946, cautery excision of the exteriorized loop was performed. The remaining colonic stoma was closed about four months later, on Oct. 18, 1946.

Surgeons who are skilled in surgery of the colon are agreed that the cure of most patients with complicated lesions of diverticulitis resides in a multiple-stage procedure, such as colostomy followed weeks or months later by resection of the involved portion of colon, with end-to-end anastomosis, or by exteriorization of the involved segment of bowel. Closure of the colonic stoma or stomas, as the case may be, subsequently is accomplished when all healing is completed.

As a general rule, when the diagnosis has been made, the preliminary procedure should be colostomy, carried out at some distance proximal to the lesion and preferably in the transverse colon. Usually, the inflammatory reaction subsides rapidly as relief of the obstruction takes place. The question as to whether the colonic stoma later could be closed without subsequent resection has been debated for many years. It is thought that if one year to two years have passed and all clinical, roentgenologic, and proctoscopic evidence of inflammation has disappeared, then the colonic stoma might be closed. The incidence of recurrence after closure of the colonic stoma still seems to be too high, and it would appear that resection should be performed in a few weeks after colostomy. Pemberton, Black, and Maino reported that in thirty-eight

instances of closure of the colonic stoma, there were two deaths postoperatively, and twenty-three of the remaining thirty-six patients experienced recurrence of the diverticulitis. Such a rate of recurrence would seem to indicate that colostomy alone is insufficient treatment for complicated diverticulitis.

The surgical risk in the treatment of these complications of diverticulitis formerly was rather high. However, there has been a marked decrease in the operative mortality risk with the introduction of the sulfonamides and penicillin. Pemberton and his co-workers have shown that in a group of 245 patients treated before sulfonamides were available, the mortality rate for all surgical procedures was 14.7 per cent, whereas in a group of 144 patients treated with sulfonamides the mortality rate decreased to 4.2 per cent. Therefore, it would seem that after colostomy, removal of the involved segment of the colon is definitely indicated, and that the indications for surgical treatment in recurrent diverticulitis might be extended.

Summary

The incidence of diverticulosis is not definitely known. In 95 per cent of the cases, the disease occurs in persons 40 years of age or older. Among approximately 15 per cent of these, diverticulitis will develop. In this group complications requiring surgical treatment will develop in about one in four patients. These complications are perforation, obstruction and formation of fistula. Colostomy is the safest preliminary surgical procedure, and subsequently should be followed by resection of the involved segment of the sigmoid. The operative mortality rate has been markedly reduced by the use of the sulfonamides.

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Discussion

DR. W. WAYNE BABCOCK, Philadelphia, Pa.—It is refreshing to hear a paper on diverticulitis that really considers the cure as well as the palliation of this serious affliction. It has been surprising to me that most articles appearing up to this time upon diverticulitis of the colon have been very conservative and have emphasized the medical treatment rather than eradication of the disease.

Eight years ago two papers, one by Dr. Dixon and one by Dr. Brown, from the Mayo Clinic, reported 191 cases. The treatment advised was to watch the patient for ten days or more, and if he became worse to do a colostomy proximal to the lesion and to wait a year to see if the colostomy could then be closed. The results of this plan were discouraging. Of sixty-four patients treated by colostomy, 17 per cent died of the colostomy or a related condition; and 44 per cent of those traced were not well. If an abscess developed they waited until it had localized and then incised and drained. Finally, 45 per cent had a corrective type of operation with a 22 per cent mortality. With this mortality and 29 per cent of the traced patients unrelieved, Brown concluded that surgery was inadequate, and he thought

that someone should devise an effective medical means of treating that disease. At the Massachusetts General Hospital the same temporizing type of treatment was followed and of 140 cases, seventy-seven were treated without operation, of which three died in the Hospital and two later, from undiagnosed cancer. I have seen over sixty cases of cancer of the rectum where treatment was delayed four months or more because the x-ray report was negative. The x-ray is not a dependable means for the diagnosis of cancer when associated with diverticulitis or for cancer without diverticulitis when it is in the rectum. Rectal cancer is in the blind spot for the x-ray. Only twelve of the 140 cases that were studied at the Massachusetts Hospital had the diseased area eradicated. Of fifty-five palliative operations, five patients had unrecognized cancer from which they apparently died.

Hayden concludes that diverticulitis without perforation is always a nonsurgical problem. As there was 50 per cent mortality from his drainage of abscesses, he thinks it better to let them perforate spontaneously. Rankin and Grimes, T. E. Jones, and others likewise considered acute, subacute and chronic diverticulitis to be fundamentally medical problems with complications essentially surgical. It reminds me that doctors had the same attitude as to appendicitis fifty years ago. Then T. S. Morton in Philadelphia reported the first appendectomy performed before an abscess had developed, and John Deaver is said to have commented, "I don't see anything in that operation."

Diverticulitis is so common and so often leads to serious complications that it is desirable to have a routine sigmoid and rectal examination made during every pelvic operation.

The troublesome diverticuli usually do not admit barium and therefore are not shown on the roentgen film; however, one of our patients had a perforation from the pressure of a barium enema on a thin-walled sac. Likewise, the proctoscope is not dependable, as showing the mouths of inflamed diverticuli. It is difficult to recognize the openings even in the open bowel.

Cancer is often overlooked in the diagnosis of diverticulitis, but we have seen several patients in whom the hard, diverticular mass was mistaken at operation for carcinoma.

Finally, I may mention that an occasional patient will have diarrhea instead of the usual constipation, and allude to the whistling urination as diagnostic of a perforation into the bladder.

The mortality will of course fall as early radical resections supplant the delayed palliative procedures.

DR. DAVID FINDLEY, Omaha, Nebraska.—I wish I had heard this paper a few months ago. It would have saved me no end of embarrassment, because I had two similar cases of diverticulitis within three weeks' time. Many of us are too prone to forget the other organs that may give rise to annoying if not distressing pelvic symptoms. A common question which is asked in Board examinations is, "What is the diagnosis of pain in the right lower quadrant?" But what about the pain in the left lower quadrant?

My patient, a little over 50 years, complained of pain in the left lower quadrant. Other findings were perfectly normal, the diagnosis of ovarian malignancy was made and laparotomy performed. A ruptured diverticulum was found and resection of the sigmoid performed.

The second case was almost identical. With diverticulitis clearly in mind, proctoscopic and roentgenologic examinations were made but nothing found. Laparotomy was done with the clinical diagnosis of pelvic inflammatory disease or ovarian malignancy. We found an acute ruptured diverticulitis, with a frozen pelvis. Again resection was deemed necessary.

The symptomatology of diverticulitis may easily be confused with carcinoma or other neoplasms of the ovary or pelvic inflammatory disease. It is well for us to bear this condition in mind and not depend too much on radiological findings and proctoscopic examinations.

FETAL AND NEONATAL MORTALITY: CAUSES AND PREVENTION*

WILLIAM F. MENGERT, M.D., DALLAS, TEXAS

*(From the Departments of Obstetrics and Gynecology of the Southwestern Medical College
and of Parkland Hospital)*

APPROXIMATELY 4 per cent of all fetuses and newborn children reaching a size and development compatible with extrauterine existence die before, during, or soon after birth. Representative figures are portrayed in Table I. Of these, almost one-third die in utero and one-fifth perish during the birth process. About one-half are born alive, but succumb within the first few post-natal days or weeks.

TABLE I. REPRESENTATIVE FETAL AND NEONATAL MORTALITY RATES

INSTITUTION, OR PLACE	YEAR	DELIVERIES, NUMBER	RATES, PER CENT
Long Island College Hospital ²	1940-44	7,580	2.63
New York Hospital	1935-40	25,823	3.52
Sloane Hospital ¹⁰			
Chicago Lying-in Hospital ¹⁸	1931-41	27,321	4.28
Dallas	1942	8,691	3.94*
Texas	1942	—	5.36
United States	1942	—	4.04
Connecticut	1942	—	2.92
New Mexico	1942	—	9.79

*Dallas: Rate for whites, 3.12; Negroes, 7.35; Mexicans, 8.65.

Although figures, standards, and methods of calculation vary, it would seem reasonable to state that the principal over-all cause of death is anoxia,^{2, 10, 12, 18} with immaturity ranking second in importance (Table II). Birth injury and congenital malformation vie for third and fourth place, while infection completes a quintet of chief hazards.

TABLE II. PRINCIPAL CAUSES OF FETAL AND NEONATAL DEATH
(Relative Per Cent)

	NEW YORK HOSPITAL SLOANE HOSPITAL, ¹⁰	CHICAGO LYING-IN HOSPITAL, ¹⁸
Anoxia	19.8	28.7
Prematurity	18.5	14.4
Congenital malformation	14.1	11.1
Birth trauma	11.6	13.0
Infection	8.1	4.7

The causes and prevention of fetal and neonatal mortality will be discussed under three main headings according to time relationship to birth.

Intrauterine Fetal Death

Unfortunately, the basic causes of intrauterine fetal death remain largely unknown. About one-half of the children dying in utero become macerated,

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and ultimate examination is difficult. Nevertheless Potter and Adair¹⁸ found evidences of anoxia in about one-fourth of all fetuses perishing before birth. Beck² and Greenhill¹² concur in the belief that interference with the function of tissue respiration is responsible for many intrauterine deaths. Partial placental separation is the most obvious and understandable cause, although it does not begin to explain all fetal oxygen deprivation. There are many other causes of intrauterine fetal oxygen deprivation, including such maternal conditions as pneumonia, cardiac decompensation, anemia, and pituitrin stimulation. In passing, it is worthy of note that the cyanotic and club-nailed congenital cardiac and her fetus are habituated to chronic oxygen lack and seldom harmed by it. Finally, the possibility that high altitude flying may cause oxygen deprivation must be mentioned. There is a dearth of factual information concerning this and, therefore, real need for scientific research.

Premature Labor.—Arbitrarily selected series to illustrate the incidence of premature labor are presented in Table III. Strictly speaking, death resulting from immaturity occurs intra partum or in the neonatal period. Nevertheless, the cause relates to pregnancy and not to labor. We are aware of increased incidence of premature labor with certain specific conditions, including toxemia, multiple pregnancy, antepartum hemorrhage, and infection. Less well known is the effect of intercurrent maternal illness of nonspecific nature, and of dietary and economic influences.

TABLE III. INCIDENCE OF PREMATURE TERMINATION OF PREGNANCY

	DELIVERIES, NUMBER	YEARS	INCIDENCE, PER CENT
New York Hospital ⁹	31,900	1932-43	2.95*
Philadelphia Lying-In ²⁰	33,668	1930-44	8.8†
Cincinnati General Hospital ³	13,526	—	10.9†
Parkland Hospital, Dallas ¹⁴	4,123	1944-46	11.3*

*1,500-2,499 grams.

†Less than 2,500 grams.

Brown, Lyon, and Anderson⁵ found only a small difference between the incidences of prematurity in patients with, and those without, toxemia. On the other hand, the incidence soared from 9 to 20 to 47 per cent when toxemia was classified into three grades of increasing severity. Dana⁹ found toxemia to be the principal cause of immaturity, with multiple pregnancy second. Slight uterine bleeding or even spotting without apparent cause is sometimes associated with premature expulsion of uterine content.^{6, 9, 10, 12} The association increases in significance as bleeding becomes more severe. More than one-half of all patients with clinically recognizable premature separation of the normally implanted placenta give birth to immature children. On the other hand, placenta previa is not as much of a causative factor of prematurity as the treatment directed at it. Nevertheless, the result is identical. The prematurity rate among women with various chronic diseases is several times as high as among those free of complication.^{3, 7, 11} Environmental factors also affect the termination of pregnancy. Thus, Dana⁹ found more than three times the incidence of prematurity among ward, as among private patients. Parkland Hospital in Dallas¹⁴ caters almost exclusively to an indigent clientele and has the highest incidence (11.3 per cent) of prematurity of those institutions listed in Table III. Moreover, three-fourths of the Parkland patients are Negro or Mexican, with extremely poor diets judged by any standard. Protein deficiency is universally evident, and pronounced in some of them. It may be that the poor dietary and social environment accounts, at least in part, for the high incidence of prematurity. Tyson²⁰ believes that dietary deficiency has much to do with

increasing the incidence of immaturity. A group of 750 expectant mothers was given a special diet containing large amounts of proteins, vitamins and minerals with definite limitation of fluids. Not one instance of prematurity occurred, but there were thirty-seven premature births in a control group.

Syphilis used to be a prominent cause of premature birth and stillbirth. The employment of serologic tests for syphilis as part of routine prenatal care, with prompt and efficient treatment when indicated, has materially reduced its prominence.⁴

It would hardly be fair to close this section on Intrauterine Fetal Death without mentioning that autoimmunization by the Rh factor is both relatively and numerically insignificant from the etiologic standpoint.¹⁸

Intrapartum Death

The chief causes of death during labor are: anoxia, malformation and birth injury, principally intracranial hemorrhage. Other etiologic factors include: intrapartum infection¹⁶ and improper choice of method of delivery.

There is universal agreement^{2, 10, 12, 18} that anoxia, resulting in fetal asphyxia is the principal cause of intrapartum death. Moreover, many asphyxiated infants are born alive, only to die neonatally. This will be discussed later. Asphyxia during labor may result from direct interference with the oxygen supply to the child or through some mechanism producing central depression. One factor may produce the other. Thus, intense and prolonged uterine contractions may not only diminish the fetal oxygen supply directly, but also may compress the fetal head. Moreover drugs administered to the mother may produce maternal narcosis and exert a direct depressive action on the fetus. Of the two main factors, direct interference with the oxygen supply during labor is likely to result in fetal death more often than a central depressive mechanism.

According to Murphy¹⁵ 0.7 per cent of fetuses surviving intrauterine existence will be stillborn or succumb shortly after birth because of malformation. These deaths, of course, are unpreventable.

Many types of injury occur during birth. Nevertheless, that most commonly fatal is intracranial hemorrhage, generally resulting from tentorial tear. Except when intracranial injury results from prematurity, it is largely preventable.

Recently Odell and Plass¹⁶ reported that sixty-nine (39 per cent) of 187 infants of mothers suffering with fever of infectious origin during labor were stillborn or died soon after birth. Maternal intrapartum fever, therefore, is an important cause of fetal death and should be vigorously combated with chemotherapeutic or antibiotic drugs.

Obstetrics is an important branch of Preventive Medicine. Among patients receiving adequate prenatal and delivery care, the obstetric emergency is virtually a thing of the past. Brutal operations and the desperate eleventh-hour fight to save a life (so dear to our lay friends in Hollywood) represent, in most instances, failure to anticipate and plan for eventualities. When such desperate situations arise, the desire to save fetal life must not become so overpowering that an operation hazardous to the mother, and in itself often fatal to the child, is performed. In 1931 Plass¹⁷ cautioned against the "exaggerated idea of the value of an infant's life as compared with the life and health of his mother." Nevertheless, operations in themselves especially hazardous to the child, as well as dangerous to the mother, continue to be performed. In some instances, operations with no other excuse for performance than fetal salvage are done when the infant is *already known to be dead!* This was true in Germany in 1928 when Winter²¹ reported that 178 cesarean sections, performed

for reasons which could be classed only as fetal, were begun *after* the operator recognized fetal death. It is true in the United States today, when a patient with prolapsed and pulseless cord is managed by abdominal delivery. The fallaciousness of such obstetric philosophy is also reflected in the growing employment of abdominal delivery. Modern incidences of cesarean section range upward as high as 10 per cent, and many reputable physicians and clinics deliver one in twenty women by the abdominal route. Yet Aiken¹ reports that while there has been a striking improvement in the maternal mortality rates of cesarean section, the fetal loss remains unchanged. A representative figure is about 8 per cent. It is within reason to believe that many infant lives will be saved if the physician makes an objective, statistical appraisal of survival chances in advance.

Neonatal Death

Almost half of the total fetal wastage occurs after birth, although the genesis of most of these deaths occurs during labor. The principal causes of neonatal death include cyanosis and atelectasis, anomalies, birth injury, and infection. Almost three-fourths of the children dying during the neonatal period succumb during the first twenty-four postnatal hours. Thus it is evident the death relates to labor and the obstetrician must accept the responsibility.

Schreiber¹⁰ directed attention in 1938 to the deleterious effects of apnea of the newborn. Cole, Kimball, and Daniels⁸ showed that sedatives and anesthetics increase the incidence of asphyxia of the newborn in direct proportion to the amounts given, and the duration, respectively. Beck² says, "Most of the methods which have been recommended for the relief of pain during labor may cause the death of the child if they are not given with caution." There is virtual unanimity of recorded opinion concerning this point. It is not too far fetched to affirm that relief of the pain of labor is numerically and relatively the biggest single cause of asphyxia of the newborn. It is impossible to guess how many subsequent deaths result from neonatal asphyxiation, but it may be asserted that they are largely preventable. Subsequent atelectasis remains a great problem. It may be that reduction of alveolar surface tension with substances like amyl acetate, as suggested by Gruenwald¹³ may prove beneficial.

Birth injury is largely preventable. Although we cannot always avoid prematurity, the aftercoming head, and an occasional difficult vaginal operation, we can withhold sedative drugs, employ nerve block anesthetics, and avoid the double danger of injury plus anoxia.

Summary and Conclusions

Approximately four per cent of all fetuses and newborn children reaching a size and development compatible with extrauterine existence die before, during, or soon after birth. The principal over-all cause is anoxia with prematurity ranking second in importance.

Five to 10 per cent of all infants are immature, weighing less than 2,500 Gm. at birth. The principal causes of prematurity include maternal toxemia, multiple pregnancy, antepartum hemorrhage, maternal illness of nonspecific nature, and dietary and economic influences. The principal cause of anoxia during and immediately following labor is the analgesic and anesthetic drugs administered to produce relief of the pain of labor.

Neonatal death accounts for almost half of all fetal wastage and three-fourths of this occurs within the first twenty-four hours.

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Discussion

DR. WARD F. SEELEY, Detroit, Mich.—The marked reduction in the maternal death rate that has occurred in the United States in the past few years has given the obstetrician time and opportunity to consider the other major obstetric problem—namely, neonatal and fetal mortality, a study of which Dr. Mengert has presented.

Two divisions of the subject naturally present themselves, (1) preventable and (2) nonpreventable deaths. Quite naturally, the chief immediate concern of the obstetrician is with the preventable group as with these he might be quite rightly charged. That unpredictable deaths occur there can be no doubt, and in my experience these have been from one-third to one-half of the gross fetal mortality rate. Deaths occurring among nonviable prematures, with fetal abnormalities incompatible with life and with fetuses dead on admission, in the light of our present knowledge, cannot be charged to the attendant. It is possible that further knowledge may, in the future, make it possible for salvage in these groups.

On account of its wide implication in fetal mortality, I have been particularly interested in fetal anoxia. Much of the work of Schreiber has been done with material which is familiar to me, and offers a field for interesting speculation in the subject of prophylaxis. In general, fetal anoxia is due either to failure of the maternal organism to supply adequate oxygen, or to failure of the fetus to receive and utilize sufficient oxygen. Lack of maternal oxygen may be due to anemic anoxia, commonly the result of low oxygen concentration in anesthetic mixtures; from obstruction to maternal respiratory passages by mucous or gastric contents, or to anemic anoxia which may occur in cases of shock and hemorrhage.

Anoxia due to failure of maternal circulation may occur with low blood pressure, cardiac failure, spinal anesthesia, etc. Failure of fetus to receive or utilize oxygen may be due to prolapsed cord, interference with placental circulation, e.g., abruptio placenta. Failure to utilize oxygen even when present in the circulation in adequate amounts can be due to analgesia and to traumatic brain injury with debilitation of the brain tissues.

Schreiber has shown that lack of oxygen to the fetal brain, for even short periods, results in areas of necrosis which, while often fatal, frequently result in so-called "devastation areas" that mentally handicap the child throughout life.

While the time allotted does not permit detailed discussion of all the causes of fetal death as outlined by Dr. Mengert, it is noted that the second major factor is immaturity. It is doubtful, with our present knowledge, whether any reduction in death rate can be made in premature death rates associated with hydramnios and with multiple pregnancy. With better understanding of etiology, prophylaxis and treatment of the toxemias it may be possible to carry more babies to viability. I have been opposed to attempts to carry the nonviable fetus of a toxemic mother to viability, with a few borderline exceptions. Such attempts are frequently misdirected as the fetus succumbs to the toxemia and the mother is irreparably damaged.

The risk for the fetus of a syphilitic mother, previously so grave, has become so minimized with modern therapy as to be no longer a major risk.

The use of anesthetics and analgesics is among the controllable factors in fetal mortality. Adequate supportive measures for the mother during labor and special attention during the hot summer months should not be neglected. In operative deliveries proper choice of procedure and expert appreciation of it at the proper time are essential to low fetal mortality.

After all has been done that is possible to reduce our fetal mortality, there is an irreducible minimum that will be eventually reached. Our last 7,000 consecutive deliveries showed a net fetal death rate of 1.3 per cent.

DR. IRVING W. POTTER, Buffalo, N. Y.—This paper brings to my mind the fact that there is such a thing as a concealed prolapsed cord, and those who do not introduce the hand into the uterus will not know it is there.

DR. ADAM P. LEIGHTON, Portland, Maine.—Anoxemia is, of course, the principal accepted etiologic factor in the death of the newly born, when especially referring to the question of resuscitation. The greatest danger is in the first few minutes after the baby is born. Very few nurses and some doctors cannot differentiate between asphyxia pallida and asphyxia livida. My meager schooling at the Rotunda Hospital in Dublin, Ireland, has served me in good stead many times in such an emergency. We did at least learn to resuscitate the newborn, when born in asphyxia. The present-day attempts of nurses in the use of a mucous catheter are pathetic. They don't know the technique, and many of the mucous catheters are no good anyway. If you want a good mucous catheter, buy a Carton catheter, an all metal instrument, with separating bell, such as has been used for years at the Rotunda Hospital, and instruct your nurses and interns to use it. As soon as a baby is born, hold the child up by his legs and slip the curved fenestrated end down over the dorsum of the tongue, through the larynx, and suck the mucus into the bell. It is easily expelled and reinserted if needed. Get the upper air passages free and patent first of all. Then if you want to give a little oxygen with the resuscitator, all right. There is nothing more irritating or bothersome than to be doing a cesarean section, and in the meanwhile to have handed over the baby to a crowd of nurses who huddle together way over in the corner, around the "service station pump," trying to resuscitate the baby. You ask, "Is the baby all right?" The nurse will answer, "Yes, it's coming," and all the time it's going. Give me a Carton mucous catheter and a tub of hot water and I'll take my chances. I would be ashamed to go out and greet the husband after the delivery and tell him that the baby died of "asphyxia," or maybe "pulmonary edema," or "atelectasis," when I knew mighty well that it was the improper attempt at resuscitation in the hands of some amateurs that caused his death.

DR. G. W. GUSTAFSON, Indianapolis, Ind.—In handling anoxia, we should use more oxygen during labor, particularly in the cases of cord compression and in the lesser degrees of separations of the placenta. Administration of oxygen to the mother will usually give a much better fetal heart rate in a shorter time, and is the quickest response we have to any therapy. This may be the difference between having a live baby and a dead one. Also, we have found that the administration of oxygen during the anesthetic will add very materially

to the rapidity with which the baby breathes when he is born. An hour's ether anesthesia given while oxygen is administered is very different from that without additional oxygen.

DR. J. BAY JACOBS, Washington, D. C.—Anoxemia has been emphasized as an important cause of fetal death, especially in premature infants. I think often anoxemia occurs in babies that are somewhat premature, possibly not according to recognized standards, but in those that are two or three weeks from term. We see this occasionally, even in the hands of those who try to regulate the dosage of analgesic drugs during labor, so I do not feel that all cases of anoxemia—especially those occurring in babies that are slightly premature—are due to improper use of analgesic drugs. The fact that they are just a little bit before term may be an important factor in causing atelectasis. At this particular time most of these babies survive, but occasionally one is lost.

Another factor in preventing intrauterine death, which I recognize as an important one, is the treatment of syphilis in pregnancy. About fifteen or twenty years ago while directing a home delivery service, I noted that only about 10 per cent of the patients had had prenatal care, and also that each month we had a few macerated fetuses to report. About ten years ago we began to round up all indigent pregnant women and were very successful in educating them to the importance of prenatal care. We instituted proper facilities in our prenatal clinics so that patients would not have to go to a separate clinic for the treatment of venereal disease, as was formerly the custom; as a result of this, we found that the stillbirth rate diminished quite markedly. I might say that in a period of ten years, from 1936 to 1946, which are the last available figures, the stillbirth rate was reduced from 38.2 to 23.9 per thousand livebirths; and deaths under one month were reduced from 40 to 27.9 per thousand livebirths for the corresponding period. I attribute this to the treatment of these indigent patients, most of whom were Negro; and it is in that group that you get most mortality, because they are the ones who are less likely to receive adequate medical care.

In regard to maternal mortality, I wish to emphasize the fact that the women who do not get adequate maternity care will raise the mortality in any State. We have reduced ours from 6.5 per thousand livebirths in 1936 to 1.2 in 1946.

DR. GEORGE W. KOSMAK, New York City.—I regard Dr. Mengert's paper as a very important contribution to the literature on this subject. However, I am rather disappointed in the discussion by others that no special stress was placed on anoxia as a factor in fetal deaths.

I would like to ask Dr. Mengert whether he feels that there has been an increase in the number of cases of fetal anoxia since the wider employment of the sedative drugs, particularly the barbiturates. As an editor, I am very much embarrassed to acknowledge the number of papers that I have published in the *JOURNAL* dealing with this, that, and the other sedative drug given in labor. According to the authors, they are all perfect. They report one, two, or three hundred cases without any fatal results. I cannot question those statements because these contributors are undoubtedly truthful people. And yet we find, notwithstanding all these favorable reports, that there are a great many cases of anoxia for which no other cause can be found.

It seems to me that something can be done by propaganda, especially through the national obstetric societies, to develop a better state of appreciation among the profession at large and among the public so far as these sedative drugs are concerned.

It is unfortunate that routine administration of barbiturates prevails in many, particularly private, hospitals. On admission patients are given routinely the favorite sedative of their physicians, usually without the latter having seen them. A painless labor has been promised without consideration of the immediate or specific needs. The amnesic effects of the barbiturates are acknowledged—the patient may brag about having had the baby in her sleep. But what about the effect on the baby? This is not always truthfully noted. This is rather a serious matter because anoxia is undoubtedly the underlying cause for a number of disturbances in babies which may not manifest themselves immediately and these babies

are pronounced perfect after their birth, since apparently no effect of the sedative drug is observed, but later they may develop cerebral conditions that are irremovable and last them throughout their lives. So I hope some word may go forth and action taken against the routine administration of these sedative drugs.

DR. ARTHUR H. BILL, Cleveland, Ohio.—Much has been said by the discussants about the bad effects of analgesia and anesthesia in contributing to fetal mortality, but I feel that I must disagree and should point out some of the good effects. I am sure that with the proper use of these procedures patients may be carried through a comfortable labor without increasing fetal mortality. On the contrary, in some instances they may have prevented fetal death. Let me illustrate as regards analgesia during the first stage of labor. In general practice, when pain is not relieved the doctor has in very many instances attempted to deliver the baby when conditions did not warrant this, usually to terminate the patient's suffering. Many stillbirths resulted. When the patient is made comfortable one is content to allow labor to go on to complete dilatation and a successful termination. This advantage certainly offsets some of the criticism.

If, during the course of hard labor, the baby is in distress one should not conclude that the anesthesia is the cause. On the contrary, the baby may benefit by the administration of more anesthetic. For example, if the fetal heart slows down to 80 or 90 beats per minute there is abnormal pressure on the baby, by the excessive contraction, likely pressure on the cord. In such a case deeper anesthesia should be administered sufficient to abolish uterine contraction with the probable result that the fetal heart will return to a normal rate. The anesthetic has removed the abnormal pressure and saved the baby. Again, consider a case in which in the latter part of labor there occurs an abnormal amount of "show," and the fetal heart rate increases say to 180. There is a beginning separation of the placenta which will probably become complete with the death of the baby if contraction continues. The immediate treatment should be the administration of complete anesthesia and delivery. Do not attribute the rapid heart rate to the anesthetic. In both of these illustrative cases the anesthetic will prevent fetal death. There are many others. I am firmly convinced that with the proper conduct of comfortable or painless labor we have not increased fetal mortality.

DR. EDWARD L. CORNELL, Chicago, Ill.—A plea for analgesia is not the primary cause for many of these cases of fetal mortality. I want to say that if you permit a nurse to administer these drugs without supervision, why not give her a medical degree? The physician should do the prescribing. If there is not enough help available it is about time to change that situation so that you can have a medical man look after the administration of drugs and not delegate these things to nurses. Nor should the routine analgesia, or whatever may be used, be delegated to a nurse. That is the medical man's province and should continue to be. There should be a medical man on twenty-four-hour duty to handle the cases of delivery. All of these patients should have good medical care, and it should not be left to the nurse to solve such problems.

DR. MILTON SMITH LEWIS, Nashville, Tenn.—I am probably one of those obstetricians whom Dr. Kosmak referred to as "the user of relatively large doses of barbiturates for relief of pain during labor."

We will report our results in 3,000 cases at the Southern Medical Association meeting in Baltimore. That this method of analgesia and anesthesia has actually been accompanied by a low stillbirth and neonatal mortality in our hands is unquestionable. Difficulty in the management of occipitoposterior positions, the incidence of midforceps and cerebral hemorrhage and other birth injuries have been markedly reduced on our service.

We believe adequate sedation permits a more conservative policy in the conduct of labor, because it not only guarantees sufficient rest for the patient but it eliminates pressure from the patient and her relatives for early interference and termination of labor.

DR. MENGERT (Closing).—It is impossible to attempt to cover all of the points raised by the various discussors. Dr. Leighton may be pleased to know that we have no

resuscitating machine. We have an old-fashioned idea that students will not have access to machines when they go into practice, and generally must learn to resuscitate babies by simpler means.

The terms "asphyxia livida" and "asphyxia pallida" have been used here. Of course, there is no such thing as "asphyxia pallida." The oxygen lack in the pale and limp baby is due primarily to injury and not to asphyxia itself. Here we have the picture of a traumatized and shocked infant. Generally the injury is intracranial. The infant is limp, pale, and has a rapid thready pulse, because he is in profound traumatic shock. I wish we could get rid of the term "asphyxia pallida." I believe that if you cannot resuscitate the baby by warmth, gentle handling, a clear airway, and the use of oxygen you cannot resuscitate him at all.

Dr. Jacobs spoke of the premature baby. We should add to that the statement that if there is any suspicion of impending premature labor, it is of vital importance that we employ analgesics sparingly.

Dr. Kosmak asked about the figures on anoxia since the advent of the barbiturates. I have no figures on anoxia in relation to the barbiturates, but Snyder and Rosenfield showed that barbiturates administered to pregnant rabbits depressed the intrauterine respiratory motions of the fetuses more than any other drug, and Henderson believed that the barbiturates produced a block of the regulation of the respiratory center.

I believe that Dr. Cosgrove, in his discussion of a paper this morning, gave the best answer to the questions and to the points raised by Doctors Cornell and Bill. Paraphrasing his answer, of course there will not be any increase of the fetal mortality rate with the use of anesthesia and analgesia in the hands of master obstetricians, but in the hands of the general medical group of the country there will be an appreciable increase in fetal death rates. I have known instances where as much as twenty-five grains of nembutal were given a mother during the course of labor. Such practice often repeated will undoubtedly influence the mortality rates of the newborn infant.

CARCINOMA OF THE CERVIX IN AN URBAN POPULATION*†

A. W. DIDDLE, M.D., AND T. R. BENNETT, M.D., DALLAS, TEX.

(From the Departments of Obstetrics and Gynecology, Southwestern Medical College, Parkland Hospital and Baylor Hospital)

THIS report gives a cross section of experience in treating cervical carcinoma in Dallas, Texas, from Jan. 1, 1936, to Jan. 1, 1946. The age distribution, the amount of time lost by patient and doctor between the onset of symptoms and the diagnosis of cancer, the frequency of inadequate or inappropriate methods of treatment and their relation to sequelae are stressed.

Method

This study was begun by reviewing records of carcinoma of the cervix in the metropolitan hospitals in Dallas for the period 1936 to 1946. Many of the records were worthless. Often nothing but the name of the patient, the date of admission and discharge, and the clinical diagnosis were given. Additional information was obtained by cross-checking with the private radiologic clinics, which treat most cervical carcinoma, and the Registrar of Vital Statistics of the City of Dallas. For nearly two-fifths of the patients dying of cervical cancer in the city the primary cause of death was reported as carcinoma of the uterus or fundus uteri, or no mention was made of cancer. These results indicated the vital statistics were not an accurate index of cancer deaths. Finally the files were checked in four of the main pathology laboratories in the city. Records from these were excellent. Through the various channels described, data were obtained for 1,134 women who clinically had carcinoma of the cervix. It was believed these represented at least 90 per cent of the new patients seen with cervical cancer in the city during the ten years. The succeeding discussion is based on 992 women for whom the histologic diagnosis was available. Follow-up studies were obtained by sending a questionnaire either to the patient or to the family physician or to both, to ascertain whether or not the patient was living and whether there had been vaginal bleeding and pelvic pain after treatment. This procedure met with some passive resistance from physicians and patients' relatives. Some of the doctors felt the investigation was directed against them personally. Relatives were afraid the patient would learn she actually had cancer. These reasons plus change of address resulted in failure to trace more than one-fifth of the women. It was obvious that accurate statistical data could not be presented, instead only trends were determined. Five- and three-year survival rates were calculated, respectively, for the periods 1936 through 1940, and 1941 through 1943. The term "operable" carcinoma will refer to lesions limited clinically (Schmitz I and II) to the cervix and "inoperable" to those with extension of the cancer outside its borders (Schmitz III and IV).

Often the patient had undergone previous gynecologic operation. For the purposes of this paper it was necessary to make arbitrary decision concerning relation of previous operation to present cervical cancer. Operations performed within two years of recognition of cancer were considered done after the carcinoma appeared. If the operation antedated the diagnosis more than two years the cancer was assumed to have developed postoperatively.

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Patients

One-third of the women were referred from smaller communities in Texas, Arkansas, Louisiana, and Oklahoma to Dallas for treatment, while the other two-thirds lived in the city. The number of patients in the pre- and post-menopausal period of life was approximately equal. Eighty per cent were white and the remainder Negro or Mexican. The age distribution is shown in Table I. Note that 5 per cent of the women were under 30 years of age. Contrast this figure with others ranging from 1.37 to 4.3.¹⁻³ The youngest patient was 19 years, and the oldest 87 years of age.

TABLE I. CARCINOMA OF CERVIX, AGE DISTRIBUTION

AGE (YEARS)	PATIENTS	
	NUMBER	PER CENT
Under 30	49	5.0
31-40	182	18.3
41-50	290	29.3
51-60	252	25.4
Over 60	162	16.3
No data	57	5.7
Total	992	100.0

Symptoms

Most of the women sought consultation for vaginal bleeding or leucorrhea, while a small number gave a variety of complaints. Table II gives the duration of symptoms. It was impossible to correlate the duration with the clinical grade of the tumor. This may be a reflection of poor histories. Where the duration was known, the average delay from the onset to the time a diagnosis was made was 7.4 months; 6.4 wasted by the patient and one by the doctor. The delay was one to two months above the average for indigent and referred patients. The time wasted during 1936 and that in 1944 and 1945 was essentially similar, indicating that patients and doctors had not become more cancer conscious.

TABLE II. DURATION OF SYMPTOMS

DURATION (MONTHS)	PATIENTS	
	NUMBER	PER CENT
Under 6	442	44.6
6-12	173	17.4
13-24	65	6.6
25-36	32	3.2
No data	280	28.2
Total	992	100.0

Pathology

Sixty of the patients had adenocarcinoma and 932 epidermoid carcinoma. Table III reveals the clinical grading according to the Schmitz Classification. Frequently the pelvic findings were described so tersely that this interpretation was impossible. Many physicians made no apparent attempt to utilize any type of classification. A number of women were treated by simple total or subtotal hysterectomy. Although the clinical grade of the tumor was unrecorded for less than one-half of those totally hysterectomized, sufficient data were available to indicate that most of the lesions were operable. Two-thirds of the women subjected to subtotal with unsuspected cancer had an inoperable tumor by the time the diagnosis was made.

TABLE III. SCHMITZ CLASSIFICATION

CLASSIFICATION	NUMBER OF PATIENTS
I	57
II	171
III	302
IV	174
Unclassified	290
Total	992

Treatment

For purposes of presentation, treatment was divided into two categories: that given before cervical carcinoma was suspected is shown in Table IV, and that administered after cancer was suspected is listed in Table V. The technique of administering x-ray and radium varied, but in general a total of 3,500 to 5,000 milligram hours of radium was delivered to the cervix and parametria. Two to three thousand roentgens measured in air were given to each of two pelvic ports located anteriorly and posteriorly. Patients hysterectomized usually received external irradiation postoperatively, rarely preoperatively. Where subtotal was done originally without suspecting cancer, an interval of three to twenty-four months elapsed before x-ray or radium, or both, were given. Approximately one-tenth of the women were reirradiated six or more months after the initial series of treatments. When done, it was usually for the purpose of palliation. It was apparent that the clinical grade of the tumor was more important than the method of irradiation in determining the future prognosis. Simple total and subtotal hysterectomy were performed with about equal frequency from 1936 to 1946 for missed or proved cases of carcinoma of the cervix. Two-thirds of the totals were done deliberately after the diagnosis was established or suspected, while one-third was performed without suspecting a malignancy.

TABLE IV. ORIGINAL TREATMENT OF PATIENTS WITH UNSUSPECTED CARCINOMA

TREATMENT	NUMBER OF PATIENTS
Subtotal hysterectomy	56
Total hysterectomy	17
Oral medication	14
Local treatment to the cervix	11
Estrogens	7
No examination or medication	6
Exploratory laparotomy	5
Bilateral oophorectomy	5
Hernioplasty	1
Total	122

TABLE V. TREATMENT

TREATMENT	PATIENTS		
	TRACED	UNTRACED	TOTAL
X-ray and radium	432	98	530
Total hysterectomy and irradiation	66	23	89*
Subtotal hysterectomy and irradiation	80	19	99†
Other gynecologic procedure and irradiation	8	2	10
Information incomplete	180	84	264
Total	766	226	992

*Sixty of the total hysterectomies were performed deliberately after cancer was suspected. The other twenty-nine were done without suspecting carcinoma or the relationship was unknown.

†Fifty-six of these operations were done one to twenty-four months and forty-one, twenty-five months, or more prior to diagnosis. Information was unavailable for two others.

Blood transfusion was seldom used except in the terminal stages of the disease. Our impression was that some patients were unable to tolerate a full course of irradiation because of anemia.

Results

Five- and three-year survival rates for patients traced are summarized in Table VI. The use of both x-ray and radium gave better results than either alone or in combination with total hysterectomy. The prognosis for those women who developed cancer in the cervical stump after subtotal hysterectomy was almost as good as for those who had cervical carcinoma with the fundus present. The survival rate was decidedly diminished for those who originally had a subtotal for unsuspected cancer probably because of two factors: more time was wasted in giving proper treatment and the growth of the tumor was aggravated. Irradiation treatment gave as satisfactory results for adenocarcinoma of the cervix as for epidermoid carcinoma.

TABLE VI. SURVIVAL RATES

CLASSIFICATION	FIVE YEAR (1936-1940)			THREE YEAR (1941-1943)		
	TOTAL	NUMBER LIVING	PER CENT	TOTAL	NUMBER LIVING	PER CENT
I	21	17	81	13	11	84.9
II	50	32	64	55	33	60
III	105	31	29.5	78	30	38.4
IV	62	3	4.8	42	7	16.6
Unclassified	91	23	25.3	61	28	45.9
Total	329	106	32.2	249	109	43.9

Nearly one-fourth of the women traced had known sequelae, exclusive of pain, attributed to the malignancy or to the treatment (Table VII). Sequelae were about 50 per cent more common among patients having pelvic operations than among those who were unoperated. This relationship was particularly true where extrapelvic metastases and local recurrence with vaginal hemorrhage developed. Vaginal fistulas were three times more common among women who were irradiated repeatedly than among those given only one course of treatment.

TABLE VII. KNOWN SEQUELAE TO THE DISEASE OR ITS TREATMENT

SEQUELAE	NUMBER OF SEQUELAE
Hydronephrosis and pyelonephritis	56
Fistulas (42 vaginal, 1 abdominal)	43
Vaginal bleeding with local recurrence	33
Extrapelvic metastases	26
Intestinal obstruction or stricture	24
Pyometra	5
Miscellaneous	4
Ascites	3
Pleural effusion	1
Total	195*

*These involved 185 patients.

Comment and Conclusions

This survey shows that women treated for carcinoma of the cervix in Dallas, Texas, from Jan. 1, 1936, to Jan. 1, 1946, did not seek consultation any earlier than did those living in other parts of the United States. Miller⁴ found that

the patients admitted to the University of Iowa from 1917 to 1927 delayed going to the physician an average of six months after signs indicative of cancer appeared. Collins⁵ and Diddle,⁶ respectively, found the delay was the same between 1927 and 1933 and during 1941. Todd⁷ gave a similar experience for the University of Michigan from 1931 to 1937. Apparently the educational programs put on by the American Cancer Society are not sufficiently inclusive or they do not reach far enough.

The doctor wasted six months in 1917 to 1927,⁴ four months in 1927 to 1933, and 2.4 months in 1941⁶ at the University of Iowa. The figures quoted by Todd⁷ and Hoge⁸ were 1.5 and 3 months. In spite of cancer campaigns waged by state and national organizations and the emphasis placed on the subject in the medical schools, results presented indicate there is still room for professional improvement.

Ostensibly the reason for doing simple total hysterectomy was to remove the immediate extension of the growth through the cervix. The risk of extirpating the regional nodes was probably regarded too great. But experience of others⁹⁻¹² has been that even though the carcinoma may be confined to the cervix, simple total hysterectomy does not always benefit the patient. Instead it may prove to be a hazard, probably because the outer layers of the cervix are sheared off during the operation.¹³ From this analysis total hysterectomy followed by irradiation as contrasted to irradiation alone did not improve the chance for a five- and three-year survival. Actually certain types of sequelae were more common after total hysterectomy than in unoperated cases.

Five-year survival rates for cervical stump carcinoma range from 7.6 to nearly 49 per cent.^{14, 15} The prognosis appears to be poorer when subtotal hysterectomy is done in the presence of unsuspected cervical cancer. Then spread of the tumor and waste of time decrease the probability of a five-year cure. Where hysterectomy is indicated, a total properly done offers no greater risk to the patient than the subtotal, and does remove the possibility of a malignancy developing in the stump later.¹⁶

The results reported compare favorably with those collected by Miller¹⁷ and Heyman¹⁸ from different parts of the world. Yet when it is considered that one-fifth of the women received questionable or inadequate treatment, it becomes apparent that the physician carried a responsibility for results not being better. A wider use of the diagnostic curettage and biopsy and proper visualization of the cervix would have originally given more positive diagnoses of cancer. Also, the general use of orthodox therapeutic methods undoubtedly would have improved the survival rates and reduced the number of sequelae.

Appreciation is extended to all those who made this survey possible including: the physicians who furnished follow-up reports, the staff of the Bureau of Vital Statistics of Dallas, the Superintendents of the hospitals, and the Chiefs of the various radiologic, pathologic, and obstetric and gynecologic services.

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Discussion

DR. JOE V. MEIGS, Boston, Mass.—Dr. Diddle's analysis of the patients with cancer of the cervix in Dallas is of considerable interest. He was able to discover certain important facts in his 1,134 cases. The usual lack of data is obviously present in Texas as it is in many communities where there is no special group treating this disease. The treatment of cervical cancer should be confined to those groups of men who are interested and who have available all proper methods of treatment. Radiation treatment is very complicated and should be a very painstaking maneuver. The surgery of the early case and the surgery of the lymph nodes should be done by those surgeons who are truly qualified to carry out the procedures.

Supravaginal hysterectomy for cervical cancer has been done many times, and at the Pondville Hospital we have had two patients in the hospital at one time who had advanced cancer of the cervix upon whom a supravaginal hysterectomy had just been performed. This is inexcusable. Total hysterectomy except for possible cancer in situ should be condemned, for it will not cure the disease, and makes the future treatment very difficult. X-ray and radium in such cases are of very little value.

It is interesting to note the number of bowel injuries in the Dallas district. Twenty-four known cases is a considerable number, and in my discussions of this problem for the past two or three years I have emphasized that this is an important reason for the Wertheim operation. Certain roentgenologists from Texas are among those who have criticized this reason, for they state that they do not see bowel injury due to radiation. Recently in Colorado at a meeting a roentgenologist from St. Louis stated that he had never seen such a complication. I can say only that I am grateful to Dr. Diddle for calling to my attention that Dallas also has bowel injuries, presumably due to radiation.

I think the results of the radiated cases are satisfactory and measure up to the standard set throughout the world. I am equally sure that radiation treatment is not the only method of caring for this disease, and the next few years will demonstrate that combination treatments and selective treatment will prove definitely superior.

DR. ROBERT E. SEIBELS, Columbia, S. C.—A highlight of Dr. Diddle's presentation is that in the ten-year period from 1935 to 1945 there was no change in the stage of carcinoma of the uterus at the time the patient presented herself for definitive treatment. In other words, the patient had sought advice no sooner nor had the diagnosis been made more promptly in the last year than in the first year.

I am convinced that routine cytology studies could change the picture with relationship to diagnosis. We have found exactly the same percentage of unexpected carcinoma of the cervix in routine cytologic studies that Pund reported July 20, 1946, in his studies of cervixes removed for other than suspected neoplasm. Through cytology we have a diagnostic measure which only requires to be used routinely to discover many cases of early carcinoma which would otherwise be missed.

Whatever diagnostic significance we may finally attach to positive cytological studies, that is whether they will substitute for or only impel a biopsy, they have already focused our attention sharply on the patient with distinctly abnormal cells and may push the clinician to a diagnosis sooner than waiting for the patient to bleed or develop the perfectly obvious lesion.

Ayre has suggested a method differing from the usual technique of securing the cells from the vaginal pool: his technique is to make spreads from the cervix by means of a wooden spatula made from a tongue depressor and by this method groups of cells can be found which occasionally have the value of a true biopsy. This is an extension of the method previously suggested of using the small metal cannula with a syringe to secure cells from the fundus and cervix.

DR. DIDDLE (Closing).—Dr. Meigs said he had been accused of causing an increase in the number of cases of carcinoma of the cervix treated by operative measures. I think really these methods have been used all the time and the bad results were not associated with the Wertheim operation but with use of the simple hysterectomy.

Dr. Seibel mentioned cytology in regard to the study of these patients. The main trouble here is that the patient does not come to see the doctor often before six months have elapsed after symptoms began.

STAPHYLOCOCCUS AUREUS HEMOLYTICUS PUERPERAL MASTITIS AND INFECTIONS OF THE NEWBORN*†

LUCIEN R. PYLE, M.D., TOPEKA, KAN.

(From the Department of Obstetrics, U. S. Naval Hospital, Brooklyn, N. Y.)

THE occurrence of infections, regardless of type or severity, is always a matter of deep concern to those charged with the responsibility of an obstetric department. It is the purpose of this paper to present a series of 42 infections occurring in the Obstetrical Department of the U. S. Naval Hospital, Brooklyn, from Jan. 1, 1945, to Dec. 1, 1945. Twenty-six of these were infections of the puerperal breast. The remaining sixteen were infections in the newborn, seven of which involved the breast. *Staphylococcus aureus hemolyticus* organisms were found in every instance where a culture was taken.

Incidence

In reviewing the literature many interesting variances are found regarding the incidence of puerperal mastitis with or without suppuration.

TABLE I. INCIDENCE OF MASTITIS

	DELIVERIES	CASES OF MASTITIS	PER CENT
Heaton ¹	5,000	39	0.78
Webringhaus ²	4,000	88	2.2
Dorman ³	2,000	57	2.8
Fulton ⁴	1,404	126	9.0
Author	1,273	26	2.2

To show the lack of accord concerning the frequency of mastitis, Bland² quotes Webringhaus as reporting an incidence of 2.2 per cent, Dever and McFarland asserting that 1 per cent would be a fair estimate, while he himself thinks that one-half of 1 per cent would be more accurate. Fulton⁴ made a survey of all cases of mastitis reported in an English industrial town of 43,000 over a period of twenty-eight months. He states his rate of 9 per cent is correct, with the exception that there were undoubtedly cases of mastitis that were not seen by or reported to the public health authorities. Another interesting fact in his series is that mastitis occurred in 16 per cent of women delivered in the hospital, as compared with 3.5 per cent of those delivered at home.

Fulton⁴ states that the onset of mastitis was most common in the third week post partum, but that 45 per cent occurred in the fourth week. Dippel and Johnston⁶ agree. Several writers made the statement that the delayed appearance of mastitis was responsible for the disparity between the figures as shown in Table I, since in many clinics the patient would not return to the obstetric service for care, but would report to the surgical service or to a local physician.

In a review of the medical records of mothers delivered in the U. S. Naval Hospital, Brooklyn, from Jan. 1, 1945, to Dec. 1, 1945, the following re-admissions were found because of breast infections.

In a clinical analysis of these infections, certain characteristics were rather uniformly present. Sixteen mothers breast-fed their babies until the onset of symptoms of breast infection. Four mothers were breast-feeding their babies when discharged from the hospital, but ceased nursing within ten days of the

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TABLE II. INCIDENCE OF MASTITIS TO DELIVERIES

MONTH	DELIVERIES	MASTITIS
January	113	
February	99	
March	120	2
April	95	3
May	122	
June	123	6
July	124	10
August	131	1
September	125	4
October	116	
November	105	
Total	1,273	26

onset of breast symptoms. Six mothers nursed their babies less than five days. The appearance of breast symptoms after delivery was quite delayed, the average period being twenty-five days post partum. The shortest period was seven days, and the longest was forty-three days. Twenty-five patients had afebrile postpartum courses and were discharged from the hospital ten days after delivery. In most instances the onset of the symptoms was quite insidious, beginning with soreness and swelling near the nipple. With one exception the lesions were unilateral. Most of the patients had not more than 1 or 2 degrees of fever. Only two patients had a definite history of a chill.

On examination, in most instances there was a subareolar induration. In those cases where suppuration developed, the abscesses were almost all nearer the nipple than the periphery of the breast.

Eleven cases were seen sufficiently early to institute conservative therapeutic measures. Five of these patients received small repeated doses of low voltage x-ray according to the technique outlined by Dr. Harriet McIntosh.⁷ In addition, they received 30,000 units of penicillin every three hours. Two patients received sulfadiazine and ice packs. Fifteen patients were seen too late for conservative therapy, and they were treated by incision and drainage. Twelve of the fifteen abscesses were cultured, and all were reported positive for *Staphylococcus aureus hemolyticus*.

Winder,⁸ as early as 1899, reported four cases of suppurative mastitis in the newborn, one case of which came on after a suppurative mastitis in the mother. For treatment he advised "foment and leave alone."

In a review of the medical records of the newborn in the Naval Hospital from June 1, 1945, to Nov. 1, 1945, there was the following incidence of superficial infections.

TABLE III. INCIDENCE OF NEWBORN INFECTIONS AS COMPARED TO BIRTHS

MONTH	BIRTHS	MASTITIS	PUSTULES	PARONYCHIA	FURUNCLES
June	123	2	3	1	1
July	124	3			1
August	131		2		
September	125	2	1		
October	116				
November	105				
Total	724	7	6	1	2

In the June infections a culture of one breast abscess was positive for *Staphylococcus aureus hemolyticus*. The mother of one baby who had pustules developed a breast abscess with a positive culture for *Staphylococcus aureus hemolyticus*.

In July, two breast abscesses and a furuncle of the neck were reported positive for *Staphylococcus aureus hemolyticus*. The other case of mastitis re-

solved without drainage. The mother of the baby with acute mastitis, however, subsequently developed an acute mastitis which resolved after conservative therapy.

In August, from 131 births there were two cases of pustules. In September, from 125 births there were two breast abscesses and one case of pustules. Positive cultures for *Staphylococcus aureus hemolyticus* were obtained from both breast abscesses. None of the mothers of these babies developed infections.

Source of Infection

With only five cases of mastitis occurring out of 549 mothers delivered in the first five months of the year, our suspicions were not aroused. In fact, it was not until the last week in July when four mothers were admitted with acute suppurative mastitis in addition to the development of three cases of mastitis in the newborn that we became disturbed. This was mainly because of the delayed appearance of the cases of acute mastitis in the mothers.

In a brief review of the literature that we had available, we found one report that gave us a clue to our situation. This was a short editorial appearing in *Lancet*⁹ in 1936, which I quote:

"An outbreak of mastitis was reported among mothers at the Ilford Maternity Home associated with dermatitis among the infants. The outbreak was not confined to the Maternity Home, other cases of mastitis occurring in the district, and investigation was made more difficult by the fact that some of the abscesses did not develop until a month or more after confinement.

In every case it was found possible to identify the infecting organism as *Staphylococcus aureus*. Careful examination of all of the possible fomites gave no clue to the source of the infection. The staphylococcus, however, was found in the nose and throat of the women who fell ill with mastitis. Swabs of the mothers and the babies showed 40 per cent of the babies in the home carrying *Staphylococcus aureus* in their throats, and an equal number of mothers carrying it in their noses and throats.

The investigators thought that the probable sequence of events was: the mother carrying the organism in her nose and throat infected the baby's throat, and the baby in turn infected the mother's breast when sucking."

Subsequent review of the literature has brought out the following points. Parker¹⁰ in 1884 stressed the "epidemic influence as a predisposing cause." In 1925 Mellon, Caldwell, and Winans¹¹ suggested that outbreaks of pemphigus neonatorum are or may be from breast milk and cite some cases with early cultures to prove their point. Bland,² in 1927, stated that in 98 per cent or more of parturient patients the breast milk was found to contain all of the various types of staphylococci, or other microorganisms of the pyogenic group. Benians and Jones¹² demonstrated that of healthy mothers in the puerperium, 15 per cent harbored *Staphylococcus aureus* in their throats, and 17 per cent in the breast milk, and yet their infants came to no harm. Other authors have given percentages between these two extremes. Cass¹³ proposed a theory that, although the *Staphylococcus aureus* is constantly present in the surroundings of the newborn, it is pathogenic to only a few. When it is pathogenic to one, however, its virulence is increased, so that other infants are exposed to more virulent forms. Knott and Blaikley¹⁴ made rather exhaustive bacteriologic studies of five outbreaks of *Staphylococcus aureus* infections occurring in the Guy's Hospital in 1942. In these studies they graded the organisms by cultural methods into grades A, B, C, and D. In all epidemics, grades A and B were found to be etiologic agents, while grades C and D were considered non-pathogenic. They particularly stressed the importance of the hands and other forms of direct contact in the spread of these infections. One outbreak was attributed to nurses and attendants using a common workroom with nurses from

an adjacent surgical ward where there were draining cases. Another outbreak was caused by a nurse who had positive nose and throat cultures for *Staphylococcus aureus*. A third source was a prepartum patient admitted to the ward with a severe antral infection. Babies, nursing mothers, and attendants were victims of the infection. Benians,¹⁵ in a study of an outbreak of impetigo, states that identification of types or strains bore no relationship to pathogenicity but was of value only in correlating and identifying strains from different sources.

In addition to reviewing the literature, the chiefs of staff of two metropolitan hospitals were consulted concerning their experience with similar infections. Both of these physicians professed that they had no experience with infections of this type. After discussing our routines of breast care and nursery technique, they neither suggested changes nor additions.

With meager information at hand, it was decided to attempt to trace the source of the infections, since we felt that the before quoted editorial from *Lancet* gave us the best lead.

On Aug. 7, 1945, all of the personnel and civilian maids associated with the maternity wards and nurseries had nose and throat cultures taken.

TABLE IV. NOSE AND THROAT CULTURES—WARD PERSONNEL, AUGUST 7, 1945

	NURSES	WAVES	MAIDS	DOCTORS	TOTAL
Cultures	32	16	6	9	63
Cultures positive—S.A.H.	9	7	2	2	20
Per cent positive cultures	28.1	43.7	33.3	22.2	31.7

With this rather surprising result, we felt that every person with a positive culture should be removed from duty on the obstetric floor if possible, and replaced by personnel with negative cultures. Therefore nurses and Waves from other duty stations had nose and throat cultures taken.

TABLE V. NOSE AND THROAT CULTURES ON PERSONNEL NOT ASSIGNED TO THE MATERNITY WARDS, AUGUST 8, 1945

	NURSES	WAVES	TOTAL
Cultures taken	16	23	39
Cultures positive—S.A.H.	3	9	12
Per cent positive cultures	18.3	39.1	30.7

The fact that the percentage of positive cultures in personnel from other departments was comparable, although not quite as high as in our own personnel, made us think that the source of the infection could not be traced to a single carrier or so in our department, but that the source of infection must be more epidemic in character. A higher incidence of positive cultures occurring in the waves than in the nurses would also be positive evidence, though

TABLE VI. NOSE AND THROAT CULTURES TAKEN ON MOTHERS

	WARD E-3-S	DEPENDENTS WARD	TOTAL
Cultures taken	19	21	40
Cultures positive—S.A.H.	9	4	13
Per cent positive cultures	47.3	19.5	32.5

each group lived in quarters, the nurses were not as closely associated in living quarters, transportation, and social activities.

On August 11, all of the patients and babies on the two wards and four nurseries had nose and throat cultures taken.

These findings substantiate, somewhat, the epidemic tendencies of the infection since Ward E, 3 South was a ward composed of units of four to six

TABLE VII. NOSE AND THROAT CULTURES TAKEN ON NEWBORN

	WARD E-3-S	DEPENDENTS WARD	TOTAL
Cultures taken	21	24	45
Cultures positive—S.A.H.	3	5	8
Per cent positive cultures	16.6	20.8	18.7

beds, whereas the Dependents Ward contained only private or two-bed rooms.

The series of cultures in the newborn is interesting from two standpoints: First, there was a lower incidence of positive cultures in Ward E, 3 South, where there was the highest incidence of positive cultures in the mothers. Second, the pediatrician who took care of the infants in Ward E, 3 South nurseries had a negative culture, whereas the pediatrician in the Dependence Ward nurseries had a positive culture. Incidentally, he had had a carbuncle shortly before the outbreak of the epidemic and he also developed an infection on his hand from which a positive culture of *Staphylococcus aureus hemolyticus* was obtained. He continued to have a positive nose and throat culture after treatment had been instituted.

Cultures from the nursery floors, bath tables, soap dispensers, etc., were repeatedly negative.

Control Measures

With this information at hand, the necessary measures to control the spread of the *Staphylococcus aureus hemolyticus* infections were considered. Closing down the ward to new admissions was discussed, but this did not seem to be the answer unless the personnel were treated at the same time. Therefore, the following measures were decided upon and instituted.

1. All nurses and Waves with positive cultures were replaced with similar personnel with negative cultures.

2. All of the personnel were required to wear clean masks when caring for a patient or entering her room.

3. All of the babies who had positive nose and throat cultures and babies of mothers with positive nose and throat cultures were removed from the breast and formula fed in the nurseries.

4. The nursery routines were reviewed and their importance stressed. The walls and equipment were thoroughly scrubbed.

5. All of the personnel with positive nose and throat cultures were required to report to the nose and throat department twice daily for treatment until negative cultures were obtained. It was decided that penicillin spray would probably be the most effective form of therapy.

6. All of the personnel were cultured at ten-day intervals.

Results

The results of the measures instituted were noted almost immediately. Of the 131 mothers delivered in August, only one developed a breast abscess, as compared with ten of the 124 delivered in July. In August there were two cases with pustules in babies as compared with one abscess in the neck, two breast abscesses, and one acute mastitis in July.

This table gives the repeat cultures on nurses, maids, and doctors who had previous positive cultures and were under treatment for the same.

TABLE VIII. NOSE AND THROAT CULTURES

	NURSES	WAVES	MAIDS	DOCTORS	MOTHERS	NEWBORN
Cultures taken	73	16	8	8	43	45
Cultures positive—S.A.H.	8	4	1	1	7	3
Per cent positive cultures	13.6	25	12.5	12.5	19.4	6.6
Per cent positive cultures on first cultures	28.1	43.7	33.3	22.2	32.5	18.7

About September 15, the required wearing of masks in earing for patients was dispensed with. No infection developed in either mothers or babies delivered during the first fourteen days of September. It is interesting to note, that, in the patients delivered between September 13 and September 24, following the time when the restrictions were lifted, in babies there were two cases of breast abscesses and one case of pustules and in the mothers there were four cases of breast abscesses. During the last five weeks covered by this report there were no new cases of *Staphylococcus aureus hemolyticus* infection in mothers or babies.

Conclusions

In conclusion there has been presented: first, a series of forty-two infections occurring in mothers and newborn babies, in which positive cultures of *Staphylococcus aureus hemolyticus* were obtained in all of the sixteen instances where cultures were taken; second, the methods used in attempting to ferret out the source of the infections; and third, the measures that were instituted to control the infections.

Although this series was small and the cultures on patients and personnel were less frequent than was desirable, the evidence as presented would seem to indicate that the source of these infections was from asymptomatic carriers harboring the *Staphylococcus aureus* organism in their nasopharynx, to mothers or babies, or both.

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Discussion

DR. LESTER A. WILSON, Charleston, S. C.—That Dr. Pyle's reported incidence of mastitis of about 5 per cent in June and of 8 per cent in July is much higher than is usually the case. In a series of 1,000 consecutive private cases followed through lactation, I found an incidence of breast infections in the mother of three-tenths of 1 per cent, and in the infant the incidence was one-tenth of 1 per cent. One case of breast abscess in a newborn was due, I concluded, to a practical nurse or to an impractical grandmother who massaged the breast with castor oil to reduce the swelling which had resulted from congestion so frequently seen in the newborn.

This report again demonstrates the fact that practically all epidemics in maternity wards are human borne, and that the vast majority of them come from the upper respiratory tract of an attendant. The chief exceptions are epidemics caused by the intestinal flora now so prevalent in nurseries.

After I had read Dr. Pyle's paper, I asked a bacteriologist and epidemiologist the following questions:

1. Why were there no puerperal infections of the genital tract, when breast infections and symptomless respiratory tract carriers were so prevalent? He replied, and I quote, "I am certain that there are strains of pathogenic organisms, especially staphylococci, which

develop a predilection for certain tissues. In this epidemic, the predilection was for epithelial tissues."

2. Why did the infections of the breast become manifest about twenty-five days post partum and about fifteen days after hospital discharge; was this contamination acquired in the hospital? The bacteriologist stated that he agreed with Dr. Pyle in his deduction that the infection must have been carried to the mother's nose and throat where it remained until conveyed in some manner to her breast.

The original source of the respiratory infection in Dr. Pyle's series is speculative. I am inclined to agree with him when he states that the evidence would seem to indicate that the infections came from asymptomatic carriers of a virulent strain of *Staphylococcus aureus hemolyticus* in their throats. I suspect that the ultimate source of the infection was probably the attendant who had a carbuncle and an infected hand.

I recall an epidemic of impetigo in one of our nurseries some years ago that immediately disappeared after we discharged a maid who was carrying supplies to this nursery and who had a low grade skin infection on a covered part of her body.

It is wise to begin to search for possible human carriers, just as soon as an infection of any type appears in a maternity ward. A system of routine inspections of the personnel of our maternity wards would seem to be wise.

DR. GEORGE W. KOSMAK, New York, N. Y.—Could Dr. Pyle give us some information about the nipples in these patients? I do not believe he made any reference to that.

DR. FREDERICK H. FALLS, Chicago, Ill.—This careful study of staphylococcus infection in a maternity ward should not be allowed to go without more discussion. Dr. Pyle is to be congratulated on the zeal with which he went after this epidemic and ran it down.

I have been interested in pemphigus neonatorum since 1915 when a series of epidemics in Chicago were studied by me and I found the organism which had been previously described as the cause by Clagg and Wherry working in the Philippines. Before that these organisms were said to be streptococci. The organism is like a streptococcus in smear, but when cultured it is found to be *Staphylococcus aureus*. I cultured it, put in my own arm, and produced a typical lesion and recovered the staphylococcus from the lesion in my arm, which fulfilled the requirements of Koch. Since then I have been interested in learning where these epidemics of pemphigus come from, and it is important to remember that a pemphigus lesion may come from a nonpemphigus lesion. I think there is no question that the obstetrician with a carbuncle or infected hand is the person to be most under suspicion in connection with this epidemic.

Furthermore, I have shown this in the study of a breast abscess that occurred in a newborn. When I was at the University of Iowa one of my associates was demonstrating the "witches milk" in a male infant's breast. He squeezed the breast, and in about twenty-four hours there occurred a breast abscess and near that, after the abscess had been opened in two hours a pemphigus neonatorum lesion occurred showing the relation between the two types. And of course in the abscesses in the mother that are associated with epidemics of pemphigus is well known. They had to close the ward in the county hospital at one time because of an epidemic. We found that one of the night women who passed the babies out to the mothers had severe acne. The disease was totally unsuspected or that she was the source of the epidemic, but as soon as she was eliminated from the ward the cases of pemphigus disappeared. I think that whenever a pemphigus develops in the ward we should examine the personnel, not for gross evidences of infection, but for minor things such as an acne or a hangnail or a little boil on the neck which is the probable source of the epidemic.

DR. PYLE (Closing).—In reply to Dr. Wilson concerning puerperal infections, there may have been an instance or two in that time of low grade puerperal infection. I do not have the figures on that. However, I know that the isolation wards were filled with mothers of babies who had infections. The infection of the babies occurred while they were in the hospital, whereas the mothers' infections were of the delayed type.

I cannot answer Dr. Kosmak's question about the nipples.

HYSTEROSTOMATOMY*

LOUIS H. DOUGLASS, M.D., AND JAMES H. GRAVES, M.D., BALTIMORE, MD.

(From the University of Maryland School of Medicine)

HYSTEROSTOMATOMY or the operation of cutting the cervix was first described in detail by Dührssen in 1890, although it had probably been in use for some time prior to this. His contribution to the subject was so outstanding that the operation is frequently spoken and written of as "Dührssen's incisions." This term is not only cumbersome, but does not describe what is done and should be abandoned in favor of the descriptive one, hysterostomatomy. This suggestion was also made in 1933 by Randall. It is so indexed in the ninth edition of DeLee, revised by Greenhill.

The American literature on this procedure is not voluminous, and the attitude of many of the obstetricians of this country seems to be well expressed by Stander, who states that it is "freely employed in Germany, but only occasionally in this country." The reason for this feeling is not clear, but possibly is due to unfamiliarity, not only with the operation itself, but with the postpartum cervix.

Apropos of this, DeLee, in 1927, stated that for several years he had made it a practice to routinely inspect the cervix immediately post partum and to repair all cervical lacerations. He urged at that time that others adopt this same practice, and reported that there was no increase in morbidity as a result of it. The same recommendation is found in *Puerperal Gynecology* by Bubis, and in articles by Siegel, Goodhand, and others. It has been our practice for quite a number of years to follow this teaching, and we have found it not only without danger to the patient, but of decided benefit; in that many of the repaired cervixes have healed by primary union and the external os again presents a round, small opening rather than a transverse slit, or several ragged tears. Upon occasion, routine cervical inspection has disclosed an unsuspected early partial inversion of the uterus. Replacement in this phase is extremely simple and without shock. In addition to these, the operator becomes proficient, and is quite at home in the face of a cervical laceration requiring repair because of hemorrhage. And should the occasion arise to cut the cervix, he approaches the patient with confidence and with assurance.

Cervical inspection itself is rather simple, requiring only an assistant and three sponge sticks. Following the delivery of the placenta and the routine administration of the oxytocic drug, the perineum is depressed by a piece of gauze. With a sponge stick the anterior vaginal wall is raised and the anterior lip of the cervix drops into view. Grasping it and allowing this sponge stick to remain in place, it is a very simple matter to "walk around" the cervix with

*Read at the Fifty-Eighth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

the other two. Should a laceration be observed, slight traction plus retraction of the vaginal wall will almost always give adequate exposure for repair.

Practically everyone who has written about primary cervical repair or hysterostomy has recommended and, in some instances, insisted upon the use of interrupted sutures. We followed this technique originally but about seven years ago began using a continuous, lock suture. There have been no breakdown of these repairs and, after carefully comparing the result, we are convinced they are as good as when the sutures were interrupted. Certainly a continuous, lock suture is quicker and easier to put in place.

Having routinely inspected cervixes for a time, it seems quite simple to incise the cervix, when indications arise and when conditions permit. In the period covered by this report—twelve years—hysterostomy has been done at the University Hospital, in Baltimore, 229 times. These figures include seventy-eight cases reported from this clinic by Siegel in 1940. In this period 29,259 women were delivered of viable infants, so that the incidence was 1 in 128 deliveries.

TABLE I. INCIDENCE

AUTHOR	INCIDENCE
Shir	1 in 161
Randall	1 in 267
Hunt & McGee	1 in 67
Huber	1 in 100
Present series	1 in 128

Shir reports an incidence of 1 in 161 deliveries. Randall 12 in 3,200 or 1 in 267, Hunt and McGee 1.48 per cent, or 1 in 67, and Huber 1 per cent, or 1 in 100 deliveries. From this it may be concluded that the indications vary with the operator. For example, Walker states that in his hands rest and support will overcome most of his cases of cervical dystocia, and when this fails apparently has recourse to abdominal delivery. Sackett, in 1947, found that manual and forceps dilatation would usually suffice when interference was indicated in the presence of an incompletely dilated external os. Of these 229 patients, 201, or 87.8 per cent were primigravidas, and 28 had had one or more children prior to this one. So, as has been previously pointed out, the necessity for this procedure is most frequently encountered in first labors.

Of a bit more than passing interest is the fact that 146, or 63.8 per cent, were private patients, and only 83 were service. Since roughly one-half of all deliveries are of service cases, there appears a definite discrepancy here. Does fear in the more highly strung parturient cause spasm and interfere with dilatation of the external os, as Read contends? If that be true, the modern trend toward analgesia should reduce the necessity of hysterostomy. Randall felt that this was true, and in the present series we find that the incidence in the first six years was 1 in 86 deliveries, while in the second half it was 1 in 181. Only 34 per cent of the patients were under 25 years of age, 66 per cent being from 25 to 42 years old.

The indications are listed in Table II.

TABLE II. INDICATIONS

MATERNAL	ALONE	COMBINED MATERNAL
Maternal exhaustion	29	21
Lack of progress	33	10
Cervical dystocia	41	13
Uterine inertia	21	7
No indication stated	16	
Cephalopelvic disproportion	11	
Transverse lie	3	
Positional dystocia	2	
Miscellaneous (1 each)	10	
	<hr/> 166	<hr/> 51
FETAL	ALONE	COMBINED WITH MATERNAL
Fetal distress	2	17
Irregular fetal heart	7	2
Cervix about neck in breech deliveries	6	1
Prolapsed cord—2 were also breech	4	1
Meconium in vertex	4	2
Absence of 1 fetal heart in twin pregnancy	1	
	<hr/> 24	<hr/> 23

In 190 of the 229 cases it was possible to determine a single dominant indication. Of these, 166 were maternal and twenty-four fetal. It is our impression, in reviewing these case histories, that in some instances the operation was ill chosen (eleven cases of cephalopelvic disproportion, twenty-one of uterine inertia, and probably some of the sixteen in which no indication was stated). In addition there are others in which the indication as given was insufficient, and the operation probably unnecessary (irregular fetal heart, seven cases, and four of meconium in vertex presentations). The lowered incidence of the second half of the period covered by this report tends to substantiate this contention.

There were forty-one instances in which cervical dystocia was given as the indication. It is recognized that many do not agree that there is any such entity as "primary cervical dystocia," however, in our experience there does appear the occasional case of prolonged labor, for which the only explanation seems to be a cervix which refuses to dilate, and upon examination appears to be unduly resistant. It is this type of case which we have classified as "cervical dystocia."

The twenty-nine cases of "maternal exhaustion" and the thirty-three of "lack of progress" could probably be better classified. A review of their histories in some instances pointed to a different indication, but it was felt wiser to make no changes. Cervical dystocia would have been the most frequent corrected indication in these two groups. In breech presentation, usually with a small, poorly developed, or a premature baby, it occasionally happens that the body and shoulders of the child will pass through a cervix not sufficiently dilated to permit passage of the head. Here, hysterostotomy, while technically more difficult than in vertex presentations, is often the only means by which we have any hope at all of obtaining a living child. By the use of bandage scissors in this type of case the danger of injuring the baby is lessened. Reviewing the histories of the entire group it was found that twenty-five of the 229 (11 per cent) had premature rupture of the membranes, twenty had artificial rupture to induce labor (8.7 per cent), and in thirty-one or 13 per cent, the membranes were ruptured artificially before complete dilatation. Therefore in seventy-six instances, or one-third of the entire number, there was a premature rupture of the membranes.

TABLE III. DURATION OF LABOR

Under 25 hours	71	31%
25 to 50 hours	103	45%
50 hours plus	55	24%

Our criterion for prolonged labor is one which lasts for more than twenty-five hours. On this basis 158, or 69 per cent, of the total were so considered. Of the seventy-one cases in which labor was less than twenty-five hours in duration, seventeen were multigravidas, the indications for cutting the cervix being fetal.

Technique

Everyone who has written about hysterostotomy has stated that the cervical canal must be completely obliterated or effaced before incisions can be made with safety. Also, that there must be no mechanical obstacle to delivery from below. With both of these statements we are in full accord; indeed, they are so self-evident that they need no supporting argument at this time.

On the other hand, we would like to take issue, rather mildly but still rather definitely, with another statement, or possibly inference which is frequently encountered. That is, as to the difficulty of doing a hysterostotomy and the possibility of serious extensions of the incisions. Huber felt that the operation was "not without danger" of extension and of grave or even fatal hemorrhage. DeLee-Greenhill emphasize the seriousness of the operation; Beck says it should be classed as a major surgical operation and almost without exception are the difficulties and the dangers so emphasized that one finds little encouragement to undertake it. It is not our intention to claim that cutting the cervix is so simple and without danger that anyone with a minimum of training can do it with complete safety. On the other hand, it is our contention that with general obstetric experience and preparation by a period of routine inspection of all cervixes after delivery, a hysterostotomy can be done with complete assurance. The conditions mentioned earlier must, of course, be present, but when they are, the operation itself is comparatively simple.

The usually recommended locations of the incisions are at 10, 2 and 6 on the clock. Experience confirms these sites as the most satisfactory. The number of incisions and their depth naturally depend upon the amount of dilatation of the external os when the operation is begun. In some of our cases it was felt that one incision was sufficient, but in the majority two were used; and since 6 o'clock is the most awkward of the three locations, both to incise and to repair, in these the incisions were practically always at 10 and 2.

Hemorrhage following incision does not appear to be a great problem. In most of the cases in which hysterostotomy was done, the cervix appeared to have less than the usual blood supply, and bleeding from this source was surprisingly slight. Only seventeen of this series showed a total blood loss from all sources of more than 500 c.c. (7.8 per cent).

Extension to the degree that it caused hemorrhage or was difficult to repair, has been a very minor complication. A slight one did occur forty-four times, divided as shown by Table IV.

TABLE IV. NUMBER OF INCISIONS*

NUMBER OF INCISIONS	[EXTENSION OR LACERATION]	PER CENT
1— 34 cases	11	32.3
2—174 cases	33	18.9
3— 15 cases	0	0

*In six cases there was no record of the number of incisions.

On the other hand extension was confined almost entirely to the earlier cases of the series and, as experience has increased, the incidence has lessened to the point where it is now quite rare.

For the past five or six years it has been our practice to repair the cervical incisions as we repair spontaneous lacerations; that is with a continuous suture. The results of this technique have been entirely satisfactory, and there seems no reason to discontinue it. The proof of this statement we believe will be found later in the analysis of the follow-up reports.

The type of delivery and the resultant fetal mortality is shown in Table V.

TABLE V

TYPE OF DELIVERY	NUMBER OF CASES	FETAL DEATHS	PER CENT
High forceps	5	4	80
Midforceps	112	24	21.4
Low forceps	81	7	8.6
Breech extraction	23	6	26
Version and extraction	12	3	25
Destructive operation	4	4	100
Spontaneous delivery	1	0	0
Total	238*	48	20.1

*Seven sets of twins and one set of triplets.

Studying this table, several facts are quite apparent. First, high and mid-forceps operations carry an almost unavoidably high fetal mortality rate. Many of our cases so treated would unquestionably have been better handled by abdominal delivery, but, because of errors in judgment of the attending physician, admission late in labor, or other reason, the optimum time for this type of delivery had passed and forceps delivery after hysterostomatomy became an operation of necessity, rather than one of choice.

Of the forty-eight babies who were lost, three had anomalies incompatible with life, two were under 1,500 Gm. in weight, one was macerated, and one died of erythroblastosis. If we may be allowed to deduct these seven deaths, we are left with forty-one, or a corrected fetal mortality of 17.2 per cent. This does not compare favorably with some of the other reports, particularly that of Huber, with a fetal mortality of only 13 per cent.

TABLE VI. PRESENTATION

Occiput anterior	51 cases
Occiput transverse	84 cases
Occiput posterior	70 cases
Breech	25 cases
Transverse lie	4 cases
Brow	3 cases
Face	1 case
	238
In 187 instances, or 75 per cent, of the total, the presentation was abnormal.	

In this series of 229 cases the maternal mortality was 1 or 0.4 per cent.

This death occurred in 1935, the first year covered by the report. The patient was a primigravida, 30 years old, admitted to the hospital with ruptured membranes, and having been in labor some forty hours. Her temperature, pulse, and respirations on admission were 100.6° F., 120, and 28. She was given intravenous glucose and sedated, delivery being postponed. After about twenty hours, during twelve of which she slept soundly, her distress again became acute, and delivery imperative. Hysterostomatomy was done on a 6 cm.

cervix, midforeeps were applied to the head in the left occipitotransverse position, and delivery completed in twenty minutes. The child which was born alive and weighed 7 pounds 6 ounces lived only three hours, dying of intracranial hemorrhage. Some three hours after delivery, the patient "went into shock" and, despite treatment, died forty-one hours later. The final diagnosis was "toxic ileus and postpartum shock." Total duration of labor was sixty hours and fifty-six minutes. Blood loss was 800 c.c. Unquestionably this was a preventable death.

The maternal morbidity was 46.7 per cent, which does not appear to be abnormally high, when the type of case in which the operation is done is taken into consideration.

It was impossible to obtain follow-up notes on all of these patients; in 157 instances they were sufficient to be of use. The cervix was classified, as shown in Table VII, as well healed, poorly healed, and not healed. Also adhesions to the fornix of the vagina are listed. By well healed is meant that no evidence of the laceration or incision is present, and by poorly healed, a nick or small laceration was found. It was gratifying to note that 61.8 per cent of those examined could be classed as "well healed." Upon comparing the results of the repair with interrupted and with the continuous lock suture, it was found that 84 per cent of the former, and 81 per cent of the latter were classed as either well healed or healed. When the continuous suture was used, only 1 per cent of the patients showed scarring or adhesions. With the interrupted suture this figure was 5 per cent.

TABLE VII. RESULTS

	NUMBER	PER CENT
Well healed	90	61.8
Healed	32	20.4
Not healed	22	14
Adhesions	6	3.8
	157	100

There are available the records of eighty-six of these patients who have been pregnant one or more times since the operation. Balard, in 1922, reported that, in his experience, cervical incision (repaired) did not interfere either with fertility or with subsequent cervical dilatation. He thought there might be a slight increase in the abortion and premature labor rate. Shir stated that hysterostomy did not interfere with subsequent labors. Hunt and McGee and Huber reached similar conclusions.

Our findings are very much in accord with these authors. Only six abortions were encountered and one premature labor. There is no reason why a well-healed cervical laceration or incision should cause either abortion or premature labor. The incidence should be less than when no repair is done. There were no patients in this group having prolonged labor which could in any way be attributed to the previous operation, nor was sterility encountered in but one case, although many of the patients' subsequent histories were unattainable.

Of the eighty-six patients, three were undelivered, and there was one ectopic pregnancy. Of the seventy-four who delivered at term, there were seven sections, and one repeat hysterostomy. The remainder were normal with no maternal mortality and two fetal deaths.

Summary

1. Routine cervical inspection and the repair of all lacerations are simple procedures without danger, and of decided benefit to the patient.

2. Hysterostotomy occupies a definite, though limited, place in the delivery routine.
3. In this presentation, the incidence is too high, and many of these patients should have been handled differently.
4. When the operation is properly indicated, the results for both mother and baby are probably better than could be obtained in any other way.
5. When the operator has familiarity with the postpartum cervix, hysterostotomy and repair offer little technical difficulty.

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Discussion

DR. L. M. RANDALL, Rochester, Minn.—The essayist has called attention to a very useful and sound obstetric procedure. That it is infrequently to be employed does not detract from its value where the proper indications and conditions exist. Writing on this subject, fifteen years ago it was stated that hysterostotomy should not compete with cesarean section. As an antieipated method of delivery where valid indications for cesarean section exist there should be no competition; however, when the following conditions are present, namely, no cephalopelvic disproportion, engagement of the presenting part, complete effacement of the cervix, dilatation of the os to 5 cm. or more after an adequate trial of dilatation, together with maternal or fetal indications for delivery, then I believe hysterostotomy is preferable to cesarean section. In our experience it has been followed by no maternal mortality. The morbidity incident to the procedure is difficult to evaluate, owing to other circumstances usually associated with patients in whom hysterostotomy is performed.

I am not certain of the definition for cervical dystocia. Numerous factors probably are present in the case finally so diagnosed. When a parturient has labored many hours through periods of analgesia and through periods of time without pain relief, has kept in good general condition, and disproportion does not exist but complete dilatation of the cervix fails to occur, we may well be dealing with cervical dystocia. Hysterostotomy then becomes a very useful procedure, certainly preferable to manual laceration. This operation is designed to remove the impediment of the undilated cervix. The number and depth of the incisions in the cervix will be determined by the size of the presenting part and the amount of dilatation of the cervix. If one is in doubt, it seems preferable to make the three incisions at ten, two, and six and to carry them almost to the vaginal fornix. If this is done subsequent laceration of the cervix is less likely to occur. The procedure can be performed under anesthesia sufficiently light to allow uterine contractions to continue. This often results in descent of the

presenting part and elevation of the cervix after the incisions have been performed, so that subsequent trauma to the incised cervix is minimized.

The method of suture seems a matter of individual preference, but it is desirable to be certain that the initial suture secures a good bite of tissue above and at the apex of the incision. From this area bleeding most likely occurs.

Our first report on this procedure concerned an incidence of twelve in 3,200 deliveries (1 in 267). In another group sampled some years later, seventeen hysterostatomies were performed in 4,568 deliveries, an almost identical incidence. The latter group occurred when methods of obstetric analgesia and anesthesia were considerably augmented and improved, perhaps indicating that there will always be a small group of patients in which this operation will be useful.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I cannot accept an apparent endorsement of Dührssen's incisions as going out from this organization without protest, because the use of those incisions, except in the very rarest circumstances, seems to me wrong. I am one of those whom Dr. Douglass has referred to who does not believe in the existence of such an entity as cervical dystocia.

Dr. Douglass, I am sure, would accept Dr. Randall's conditions for the proper exhibition for Dührssen's operation. If he does, then the operation has eliminated the sole obstacle to delivery which he recognizes in his cases and his fetal loss should be thereby practically nothing. In his cases, therefore, there must have been other factors militating against fetal survival than the mere failure of the cervix to dilate. This is proved because he lost more than one of five babies. His paper itself would appear to me to very strongly substantiate that contention.

The trouble, I think, is that none of us is quite able to accurately meet the conditions which Dr. Randall has laid down. In my opinion, in almost every case in which the cervix is not grossly diseased, the apparent obstruction to labor which the cervix presents is in reality a degree of cephalocervical disproportion which we do not appreciate. Therefore, the cases in which we resort to Dührssen's incisions do not represent situations in which Dr. Randall's conditions are absolutely fulfilled. In the absence of gross disease, it is my firm conviction that the cases apparently held back from successful delivery by failure of the cervix to dilate depend upon other factors, which Dr. Randall has so significantly covered in his statement of conditions, not due to the behavior of the cervix at all. I make this statement in the strongest possible terms because I do not want men who are definitely less able than Dr. Douglass, Dr. Randall, and the rest of us to estimate conditions accurately to be encouraged to resort to this type of operation.

DR. DOUGLASS (Closing).—I have no argument with Dr. Cosgrove about cervical dystocia. However, there seem to be a certain number of cases where there appears to be no disproportion, and yet the cervix does not dilate. It may be due to uterine inertia or some other abnormality, but in many of these cases a simple incision of the cervix allows completion of the delivery with little difficulty.

The high fetal mortality, of course, is not due in many cases to the operation itself, but to the prolonged labor which has necessitated the operation.

VAGINAL AND RECTAL PRURITUS—ETIOLOGY AND TREATMENT*

EDWARD L. CORNELL, M.D., F.A.C.S., CHICAGO, ILL.

IT IS my considered opinion that vaginal and rectal itching is one of the most neglected fields in medicine. Too many physicians pass over the complaint with ease and give some palliative prescription, or order the patient to take x-ray treatments or a douche. This attitude is deplorable. There is always a definite reason for the itching or burning, but it takes study on the part of the physician to discover the etiology. There is no definite rule to follow in all cases. There is no patient more grateful than the woman who is permanently relieved of this distressing symptom.

This paper is based solely on knowledge obtained in my private practice. I have found vaginal itching or burning due to the following causes, the frequency being in the order named: *Trichomonas vaginalis*, thrush, trichophyton infection, *Bacillus coli* and various bacterial infections. Rectal causes have been chiefly ameba, *Trichomonas*, the molds, and *Trichophyton*. Occasionally infected hemorrhoids or ulcers of the rectum may cause the burning sensation.

Trichomonas vaginalis has been by far the most frequent type seen. This infection has been described often in the literature. From the number of treatments recommended you are already familiar with the difficulty of eradicating the disease. My thought is that the physician should become familiar with one line of attack and follow it as a routine, changing management only as failure to cure appears in the individual patient.

My procedure is as follows: The patient is instructed to insert one Devegan tablet nightly on retiring and to report for office treatment the first, third, and fifth day of the period for four periods. At this time the vagina is cleansed of blood and three devegan tablets are inserted high in the vaginal vault. After the period the patient resumes the nightly use of the tablets. No douches are used.

In my opinion douches are worthless. The vagina practically cleans itself daily, and douches only clean a portion of the vagina. The average patient will not sterilize the douche outfit, and is more apt to reinfect herself than not. Furthermore, the water used is likely to infect the vagina with the *B. coli* unless it is boiled. Most patients will not take the time nor trouble to boil the water.

After the fourth period no tablets are inserted. The patient reports back in a week for vaginal secretion examination. If the secretions are negative she reports again in a week after the next period is over. If the secretions are negative again she is pronounced cured.

Her sexual partner must be examined by a urologist. It is difficult to discover *trichomonas* in the male, and often several examinations are necessary. During the treatment of the vagina sexual intercourse should be interdicted or permitted only with the use of the condom. If, after the sixth period, the

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patient becomes reinfected following sexual intercourse without the condom, the sexual partner must have *trichomonas* in his secretions, whether found under the microscope or not.

There are patients who do not respond to the above-outlined treatment. The physician should therefore be prepared to use some other form of attack. It is best to warn the patient that *Trichomonas vaginalis* is often difficult to cure. In some cases *Trichomonas* is associated with a large number of bacteria, so that a short course of sulfathiazole is indicated. On several occasions I have found a double infection present. Usually it is thrush, but I have also found the vagina full of *B. coli*. The thrush should be cleared up first and then the trichomonas.

In the pregnant woman the disease is very distressing and incurable. The patient can be made comfortable by the use of devegan tablets.

I have never seen a case of arsenic poisoning, even where the tablets were used over a long period of time. After the pregnancy is completed, the patient is placed on the routine treatment when the bloody discharge is gone.

In patients who have no periods 100 tablets are prescribed and one tablet is inserted daily. The patient is examined ten days after she stops treatment, and again in a month. If no *trichomonas* is found, she is pronounced cured.

If the infection is still present, a course of sulfonamides is given, and the devegan treatment is repeated.

Thrush is the next common cause of vaginal itching or burning. It is usually seen as a membranous type of discharge, the entire vagina being covered with a thick yellowish white membrane which may or may not be adherent. Sometimes it has the appearance of the clumps like those seen in cottage cheese. The vagina is reddened when cleansed of the membrane. The vaginal labia may be edematous and very tender to the touch. Microscopically *monilia* are present in profusion.

Fortunately, the treatment is short, effective, and usually lasting. Two drams of sodium borate are dissolved in about one ounce of glycerine and a tampon soaked with the solution is placed high in the vaginal vault. The tampon is removed by the patient just before returning to the office for another treatment. The treatments are given daily for four days. The patient returns in a week or ten days for a check-up.

Reinfection is seen rarely. The sexual partner can transmit the disease unless the penis is thoroughly washed with soap and water previous to coitus.

While reinfection rarely occurs, one patient returned three times in a period of two months with vaginal thrush. On close questioning the patient stated that her husband had had a skin lesion on his chest for some time. In cooperation with Dr. Cleveland S. White, the vaginal secretion was cultured and also the skin lesion. They were both caused by the *monilia*. As soon as the husband was cleared, there was no further trouble with the vaginal thrush. It is another demonstration that too much attention cannot be paid to essential details to clear up vaginal infections.

During pregnancy thrush does not respond readily to treatment. It is almost impossible to cure thrush during pregnancy. There are two ways of alleviating vaginal distress. Since tampons are apt to induce abortion in the susceptible patient they are not used. One method is to paint the entire vagina with a 3 to 5 per cent aqueous solution of gentian violet. This can be done once or twice a week for an indefinite period. The occasional patient is allergic to gentian violet and the vagina becomes fiery red, denuded in spots, and very tender.

Another method is to have vaginal suppositories prepared containing 10 grains of sodium borate in each suppository. One suppository is inserted in the

vagina nightly. This will relieve the symptoms promptly. During the last two weeks of pregnancy treatment is discontinued unless the itching is unbearable.

The nursery staff is cautioned to watch for thrush in the newborn baby. Curiously, oral thrush is seldom found in the offspring of mothers with vaginal thrush.

Many women wipe themselves forward toward the vagina after a bowel movement with the result that the vagina and urinary tract may become infected with the colon bacillus. Contaminated water used for douching may also be a source. The vaginal secretions then become yellowish, thin, have an odor, and are very irritating to the labia. These patients complain chiefly of vaginal burning, although some itching may be present. The vaginal wall is often reddened and angry looking. The patient complains of pain when the vaginal speculum is inserted.

The diagnosis is made by smear and culture. If the laboratory technician is well trained, it is often possible to make the diagnosis from the wet smear.

The treatment has been simplified since the introduction of sulfonamides. One gram of sulfathiazole given every six hours for thirteen to fifteen doses usually clears the infection promptly. I have found sulfathiazole more effective than other sulfonamides. The patient is instructed to return a week after the last dose of sulfathiazole when a culture is taken. If the result is negative, she is pronounced cured. If positive, the patient is given another course of treatment.

In the occasional patient who is allergic to sulfonamides, or one who does not respond to the course of sulfathiazole, streptomycin may be used. One gram in divided doses every three hours intramuscularly for three days will usually clear up the infection.

Other types of bacterial infection seen as a cause of vaginal burning or itching, are the *staphylococcus*, *streptococcus*, and the *gonococcus*. Pain is nearly always associated with this type of infection. In some the pain is very acute, so that the vaginal speculum should be used with gentleness. In the acute case the vagina is fiery red, often edematous, and the labia are swollen and reddened. The secretions are thin, watery, and very irritating.

The source of the infection except for the gonococcus is often difficult to determine. In general, it may be stated that the infection is due to unsterile douching equipment, failure of the male to wash the penis before sexual intercourse, using saliva as a vaginal lubricant and self-examining the vagina with dirty hands.

The diagnosis is made by smears, wet and stained, and by culture using special media.

The infection responds to the sulfonamides, except that the *gonococcus* responds best to penicillin. In some cases of *staphylococcus* both sulfathiazole and penicillin have to be used.

One patient seen shortly after the close of the war developed a severe *staphylococcus* infection within a week after her husband returned from the Pacific area. It was very resistant to treatment, requiring 3,000,000 units of penicillin to effect a cure. During the acute stage the pain was severe and a prominent symptom.

Regardless of the type of infection present after the acute stage has subsided, all possible sources of reinfection should be eliminated by cauterizing erosions, Nabothian cysts, Bartholin glands, and Skene's ducts, and the urethra should receive careful attention. Fortunately, these do not give as much trouble as formerly, since the advent of penicillin and the sulfonamides.

I have seen only a few cases of vaginal infection due to the pneumococcus. The source of the infection is difficult to state, although I have the feeling it

may come from saliva used as a vaginal lubricant. The vagina has the same appearance as seen with the staphylococcus and streptococcus infections, but it is not so acutely inflamed. Fortunately, the response to sulfonamides is prompt. I have not had occasion to use penicillin.

Vaginitis is occasionally seen following the use of cauterizing drugs, such as strong solutions of silver nitrate, zinc sulfate, negatan, etc. When these drugs are discontinued the vagina clears up promptly as a rule. The vagina should be inspected frequently, however, so that the surfaces are not allowed to adhere to each other. If there is a tendency to adhere, a mild lubricating jelly may be injected daily.

Some patients are allergic to dyes such as gentian violet, brilliant green, etc. In these cases the vaginal surfaces become raw looking with more or less edema. The discharge may be profuse and it may produce a burning sensation. Soreness of varying degree is present. The injection of a mild lubricating jelly helps to relieve the pain and prevents the mucous membranes from adhering.

In women past the menopause, senile vaginitis often produces itching and/or burning. Formerly this distress was difficult to control. Now the use of estrogen by mouth usually clears the vagina in less than a month. Stilbestrol, in one mg. doses daily for a week or ten days with gradually decreasing doses will effect a cure unless there is a secondary infection with the *B. coli* or *staphylococcus*. In the latter case, sulfonamides should also be given.

The physician must rule out external causes for itching in and around the vagina. Leucoderma is not uncommon. One must distinguish this lesion from leucoplakia. In the former, itching is a prominent symptom. Also the skin and mucous membranes are cracked. These cracks are quite painful, and itching in and around them may be intense. The cracks are usually located in the folds and often extend down to the rectum. In long-standing cases the skin around the rectum may be involved.

The etiology in these cases is difficult to establish. It is my opinion that many are due to some form of mold, but I have been unable to get a growth from the lesion. I base my theory on the fact that most of these lesions have responded promptly to gentian violet applications. They have also responded to Grenz ray. Gentian violet, 5 per cent aqueous solution, is applied to the lesion and surrounding area two to three times a week for two to three weeks, and weekly thereafter until the lesion is healed. In most cases the whiteness of the skin gradually disappears. The patient should be warned that treatment may be prolonged.

In one case estrogen was used in addition to local treatment, and it seemed to help hasten recovery. Failures to cure result from inadequate treatment.

In cases not responding, a biopsy should be taken to rule out malignancy.

Another external source of vaginal and rectal itching is *trichophyton* infection. The usual source is athlete's foot disease in the patient herself or in some member of her family. I have found the *trichophyton* in the vaginal secretions in most of the patients with this type of lesion. In early cases there is a reddened, blotchy area on the labia majora varying in size from 1 cm. in diameter to a lesion 1 cm. by 3 or 4 centimeters. Cracks may or may not be present. The itching is often intense and constant. It is frequently worse during the menstrual period.

In long-standing or virulent infections the lesion may be extensive, affecting the inner aspect of the leg, the groin, the mons veneris, and posteriorly to the rectum.

Various types of medication have been used to cure the lesion. Gentian violet, 3 to 5 per cent aqueous solution, has been uniformly successful for me.

The vagina and all external lesions have been painted, usually two to three times a week, for one or two weeks, and then once a week until all lesions are gone. The feet must be cleared also because recurrence is likely to happen.

Lastly, burning and itching may be present due to lack of cleanliness. Smegma may be so profuse that the skin and mucous membrane become irritated. The lesion is seen chiefly around the area of the clitoris. Daily washing of the affected parts with soap and water is usually all that is necessary to effect a cure.

Rectal itching is a very distressing symptom, and the diagnosis of the cause is often baffling. In my private practice I have found the following etiologic factors.

When the itching is at the opening of the anus or just inside with little or no skin irritation the cause is some factor in the bowel, such as:

Ameba or other type of intestinal organism which may cause irritation with or without diarrhea. It is essential to have a cold and warm stool examined by an expert technician. It is noteworthy that these patients often have a musty straw odor which is very offensive. In the occasional case the skin around the rectum may be irritated.

Worms of various types are said to be the etiologic factor, but I have never seen a case.

The treatment of these patients is directed to clearing up the bowel by appropriate medication to remove the ameba, worms, etc., together with local treatment with gentian violet.

The second common source is a fungus growth. Here the skin around the anus is often thickened, whitish in color, and cracked usually radially from the anus. The diagnosis is readily made clinically by painting the area with 3 to 5 per cent aqueous solution of gentian violet. In a few hours the itching ceases or is markedly relieved. The dye has to be carried into the anus a short distance because the fungus infection often extends to the mucous membrane.

Occasionally it is necessary to use other medication if the patient is allergic to gentian violet. One per cent solution of brilliant green or two per cent mercurial ointment may be substituted.

Local itching or burning may result from uncleanness, especially in obese women. The treatment is obvious.

I have seen two patients who developed marked itching and a rash from being allergic to lingerie such as rayon, celanese acetate, or nylon cloth, especially if dyed dark blue or black.

Many women have the habit of dusting the vagina and rectum with talcum powder following a bath. They use boxed powder and a puff. The puff and powder become contaminated with myriads of bacteria and molds and infection of the skin follows. Discontinuing the practice and appropriate treatment will clear up the itching and burning.

The most difficult cases to clear up are seen in senile patients. I have had two. In both the lesion involved the labia, the skin in the groins and the perineum and the rectum. In both it took several months to clear the lesion. Only weak (1 per cent) aqueous solution of gentian violet must be used, because the senile skin is very sensitive to medication. In these patients moderate doses of estrogens seem to help in relieving the intense itching, especially in the vaginal area. The x-ray should not be used, as it makes the skin more sensitive to the infection. Estrogenic ointment was efficacious in one patient.

Pediculosis, scabies, and diabetes must be ruled out in all cases.

I have never seen a case of active mycosis in the vagina.

Discussion

DR. R. T. LA VAKE, Minneapolis, Minn.—This paper should be of great interest and importance to the general practitioner as well as to the specialist. It deals with conditions that can be accurately diagnosed and well handled by any painstaking physician possessing average laboratory equipment. Too often physicians underestimate the constant and extreme discomfort that these conditions entail.

Dr. Cornell brings out clearly two fundamental imperatives for success: a diagnosis by exclusion of the causes, be they systemic, due to skin diseases, or to organisms infesting the urinary, genital, or intestinal tracts; and the elimination of the male as a source of infection or reinfection.

His choice of therapy to meet varying conditions is excellent. To be emphasized is his enunciation that direct visual cleansing, followed by topical medication by direct vision, is superior to the douche. The douche does not cleanse or medicate the cervical canal which is an important harborer of infection.

In my experience, the douche itself is often the sole cause of vaginal discharge and subsequent irritation. The idea of the douche makes a rational appeal to women, especially to fastidious women. It seems to them as plausible as any type of bathing. They do not sense the primary difference, which lies in the fact that the vaginal surfaces are not dried after the douche. They fail to consider that if the hands were immersed frequently and long in hot water, particularly if the water contained chemicals advertised or otherwise heralded as beneficial for "feminine hygiene" (some of which chemicals are even commonly known to be irritating to the skin), the hands would soon become abnormal and irritated, especially if they were not adequately dried after each immersion. I believe that the douche is unphysiological. It tends to macerate the epithelium, and the mechanics of the opposing wall rolls up masses of epithelium, denuding the vagina at times even down to the papillae. These masses of epithelium break down, emitting the disagreeable odor of decaying meat, which leads to the vicious circle of more frequent douching. The douche also disturbs the normal chemistry of the vagina, disturbs the balance of life of the normal protective flora, and tends to wash out the lubricating and protective mucus.

It requires but a short explanation to convince even an uneducated woman of the rationality of this viewpoint. However, she must be warned that it may take weeks without douches before the normal healthy condition of the vagina can re-establish itself. It often takes moral support and encouragement to rid a woman of this habit. This can best be achieved by regular inspections and appropriate treatment, with encouragement as to the returning normality of the appearance of the vagina, and the return of the normal flora.

It is obvious that conditions at times present where the benefits to be derived from the understanding use of a proper douche more than compensate for its obvious defects.

In the treatment of *trichomonas* infections, two chemical preparations stand out pre-eminently as cleanly and successful: devegan and floraquin. Each contains substances lethal to the organisms, and other substances that tend to render the vagina acid, which is essential, and supply the carbohydrate requirements of the normal protective flora. Some prefer floraquin as less toxic if by chance absorbed. Strangely enough, each of these compositions will at times fail and the other succeed. At times the acid constituent is inadequate and then vinegar douches or acid jellies may be used as a temporary adjunct.

DR. ADAM P. LEIGHTON, Portland, Maine.—Amateurish and silly attempts in the treatment of many symptoms are pathetic and criminal, as for instance in dysmenorrhea and in pruritus vulvae and pruritus ani. I have come to the conclusion that women in general get little sympathy when they present themselves for relief of these symptoms. Most of the time they get ineffective treatment.

When a woman comes to me, complaining of "itching" in "front" or "back," I make it a point to see to it that she gets attention and relief. No person in the world is more grateful. A woman is made wrongly anyway from an anatomic standpoint. She is handicapped from the start in keeping clean. She may have trichomonas, sugar, colon bacteria, leucoplakia, or alkaline urine among the many causes for her itching.

A woman usually urinates all over the vulva and perineum. She ineffectually tries to dry and clean herself with paper after voiding. I find that most of these cases of pruritus vulvae and pruritus ani are due to uncleanness. Women do not use enough soap and water on their perineal region.

I have found that one of the chief offenders in these distressing symptoms is an excessively alkaline urine. This dries on the surface of the skin, and is rubbed and causes irritation by body motion and wet lingerie.

With a hyperalkaline urine, if you would restrict the ingestion of oranges, grapefruit, apples, pickles, and tomatoes, and give the woman about thirty or forty grains of ammonium benzoate a day, with a lot of water to drink, the results are surprising. It clears up the trichonitis, checks the polyuria and urinary frequency, and allays the alkalinity.

DR. WILLARD R. COOKE, Galveston, Texas.—I must take issue with one statement of the essayist that trichomonal vaginitis is difficult to cure. In about 1928 we adopted a modification of Gellhorn's suggestion, placing 1 c.c. of pure stovarsol powder in the posterior fornix every other day for six months; this to be followed after a lapse of three days by daily douches of 12.5 per cent solution of commercial vinegar in water (teacup full to one quart) for one month; twice daily during the bleeding phase of the menstrual cycle. In the first 1,100 cases in which this treatment was carried out there were six persistent recurrences. In each of these we later discovered, following a suggestion of Dr. Goodall, trichomoniasis of the endometrium and, in some instances, of the tubes. The uterus was removed from four of these patients subsequently for other indications, and in each case the vaginitis promptly responded to treatment. Without having tabulated, I would estimate that the same percentages would apply to subsequent cases.

In regard to the development of intolerance to gentian violet (I am not prepared to say whether this is an allergy) there is a very valuable warning signal which enables us to avoid giving an additional treatment after the intolerance has developed. This consists of a peculiar discoloration of the introital and vaginal mucosa which I can only describe as being between mauve and magenta. Further application of gentian violet after the appearance of this change in color will often precipitate a very painful and indolent superficial ulcerative process.

Parenthetically, and in defiance of the accepted theory of the action of succinyl sulfathiazole, we have found that vaginitis due to *E. coli* responds well to the simple repeated use of this agent in dry form in the vagina. This has enabled us to relieve a number of cases of juvenile vaginitis in which no other pathologic organism than *E. coli* could be found.

DR. J. D. GUESS, Greenville, S. C.—I wish that this paper could be published in medical journals that are read by doctors generally throughout the country, because the general practitioners see more women suffering with itching of the vulva and anus than we do, and the general practitioner has no conception of the causes or of the cure.

I was particularly interested in Dr. Cornell's advocacy of the use of borax in the treatment of vaginal thrush. I have been using it for many years.

Dr. Cornell mentioned reinfection of the vagina with thrush. Women have a practice of rinsing out underwear and putting it on again the next morning. Simple washing will not kill the *monilia*, and this practice is a frequent source of reinfection.

One other point: In my experience the most frequent cause of perianal itching is uncleanness, but not in the sense we ordinarily think of it. The passage of flatus, the accumulation of perspiration, slight seepage of moisture through the anus, excoriation in perianal skin folds occur even in women who bathe daily. The area is unclean in the strictest sense of the word. In many cases there is no other cause of itching than this moisture of the skin with slight soiling. A treatment affording temporary relief and often a cure is to massage the area with rubbing alcohol. This may be repeated at will and should be done night and morning. The alcohol is cleansing and drying. It is mildly bactericidal and it has a local anesthetic action. The patient should be warned that the alcohol will burn her for a moment.

DR. W. F. T. HAULTAIN, Edinburgh, Scotland.—This is a subject which has interested me very much for a number of years, and it would seem that our methods of treatment in Great Britain are perhaps a little different from yours. Devegán does not seem to cure by any means all cases of *Trichomoniasis vaginalis*. In Britain we see only those cases referred to us by general practitioners, and usually they have already tried devegán or some other treatment and have failed to cure the condition. Thus we have to treat the condition more intensively. I have frequently used stovarsol, which Dr. Cooke mentioned, but I think it is important that it should be given first of all as a powder insufflation, probably best given during the menstrual period, as it has been shown by Swift in Adelaide that the *trichomonas* is smallest and most active at the menstrual period, and if they are killed off then before they grow up to any size, you will have the best chance of curing the condition. Therefore, these patients are treated by dry swabbing and insufflation with stovarsol during the menstrual period, and in the interval they insert a stovarsol suppository nightly. The majority of cases clear up by such treatment.

With regard to leucoplakia, that is an important condition insofar as it is very often a precursor of malignancy; therefore, we teach that leucoplakia must not be treated conservatively for too long. If conservative treatment does not begin to cure the patient within two or three weeks, a biopsy has to be taken. In my charge during the last ten or fifteen years every patient with marked leucoplakia has had the stomach contents examined in an effort to find whether free hydrochloric acid is present or not. In about 30 per cent of the cases there was no free hydrochloric acid present in the stomach. If these patients are treated with hydrochloric acid dilute 30 minims thrice daily the leucoplakia will quickly clear up. The pioneer work on this subject was again done by Swift of Adelaide, who considered that in these cases leucoplakia was due to an avitaminosis due to the nonabsorption of vitamins A and D, and these could be added as adjuncts to the treatment.

One last comment regarding senile vaginitis. I would not consider the dosage of stilbestrol advocated by Dr. Cornell to be strong enough to obtain a speedy result. I have always given 5.0 mg. of stilbestrol twice daily for fourteen days, and on the fourth day onward have supplemented this by Kolpon pessaries (oestrone and glucose). In my experience there are very few, if any, cases of uncomplicated senile vaginitis, which do not clear up in fourteen days with this treatment.

DR. CORNELL (Closing).—I stated that I felt each physician in treating *trichomonas* should learn one individual technique and learn it thoroughly. To try first one thing and then another is a mistake. You do not get familiar with the management, the results, and the appearance of the vagina after a mixture of treatments. If you do not succeed in curing the patient with one particular method you have selected, after a sufficiently long time, then try another and become thoroughly familiar with it. I just want to caution in the use of fluoroquin in the cases that do not respond to stovarsol. Muscular pains often follow the use of fluoroquin if the patient is allergic to that particular drug.

Regarding the dosage of stilbestrol, the amount I usually start with is one milligram, and, while I do not get results as promptly as Dr. Haultain did, the results over a longer period of time are apparently equally satisfactory. I feel that in the older women we should be a little more careful of overdosing. It is easier to underdose and have the patient comfortable than to overdose and produce lower abdominal pain and other symptoms that go with overdosing of estrogens.

HISTOLOGIC APPEARANCE OF COILED ARTERIOLES IN THE ENDOMETRIUM OF RHESUS MONKEY, BABOON, CHIMPANZEE, AND GIBBON*

IRWIN H. KAISER, M.D., BALTIMORE, MD.

(From the Department of Embryology, Carnegie Institution of Washington)

THE coiled arterioles of the endometrium of the rhesus monkey undergo a series of characteristic alterations during the menstrual cycle, and play a major role in the control of the amount of hemorrhage and necrosis during menstruation. In this study these vessels are described and illustrated as they appear in routine histologic material. The loops made by the arteriole as it passes repeatedly through the plane of the section produce the arteriolar field. At the time of ovulation, the fields are in the deep third of the endometrium, and the loops are 6 to 8 in number, while the arteriolar wall is thin. In the progestational phase the loops increase in number, the fields become more superficial, and the vessel walls widen and acquire a swollen appearance. At the onset of ovulatory menstruation, there are twenty or more loops in the field which is now in the superficial half of the endometrium. These changes recede after the onset of menstruation, and the postmenstrual vessel is simple and thin walled. In anovulatory menstruation, the fields are in the deep half of the endometrium, and include about twelve to fifteen loops of relatively thin walled vessels. There is, therefore, a striking difference between the coiled arterioles of ovulatory and of anovulatory menstruation.

Coiled arterioles are found in the endometrium of the baboon, chimpanzee, and gibbon. It is possible that menstruation in the gibbon involves less hemorrhage and necrosis than in the rhesus monkey, and that the arterioles do not undergo as marked a progestational change, but there is insufficient material on which to base a definitive statement.

The concept that menstruation occurs because of ischemia produced by complexity of the coiled arterioles is untenable in view of these observations. Further studies of menstruation in other primates, emphasizing their differences from man, can be expected to clarify many of the unsatisfactorily explained features of the menstrual process.

*This article is an abstract of the Foundation Prize Thesis for 1947 of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons. It was read at the Annual Meeting, Hot Springs, Va., on Sept. 4, 1947, and has appeared in full in *The Anatomical Record*, 99: 199, 1947.

IGNAZ PHILIPP SEMMELWEIS*

PALMER FINDLEY, M.D., F.A.C.S., OMAHA, NEB.

IT HAS been said that we see far when we stand on the shoulders of our predecessors. This is but another way of saying that if we are to understand the problems of today we must know the happenings of the yesteryears—we must know history.

Carlyle tells us that history is the essence of innumerable biographies. May I offer you a biographical sketch of one of the most tragic characters in the history of medicine; a man who sacrificed his happiness, his reason and his life for an idea.

From the beginning of time stark tragedies have stalked the road to progress. In every age since history was written there have been men of vision who have evolved new ideas, new truths that have run counter to traditional beliefs and practices. Such men have too often been the targets of controversy and strife, and nowhere is this more in evidence than in the transition from primitive to modern obstetrics.

Galen, whose contributions to obstetrics were not impressive, was fiercely assailed by his colleagues, and against his adversaries he defended his theories with a vigor and acrimony that has seldom been equalled. Impatiently he turned to the laity "who," he said, "at least had common sense, which was wanting in the sophist physicians." "These opponents," said he, "differed from bandits only that the doctors practiced in Rome and the bandits in the forests."

Andreas Vesalius of Brussels was first to demonstrate that the uterus, formerly regarded as bilocular or multilocular, is, in reality, a single chamber. He literally robbed the gibbet and the grave in dissecting the body of a pregnant woman who had been condemned to the gallows. His dissections brought upon him the wrath of the clergy who contended that the body of man is the temple of the Soul and to invade it with the dissecting knife is sacrilege.

Vesalius abandoned the dissecting room and burned his manuscript. His *De Fabrica Humani Corporis* revolutionized the study of human anatomy, but was not accepted by the medical profession until long after his death.

Leonardo da Vinci, artist and anatomist of the fifteenth century, depicted for the first time the normal attitude of the fetus in utero. Drawn with the utmost fidelity to scientific accuracy and artistic beauty, his drawings were in marked contrast to the ludicrous positions which appeared in the *Rosengarten*. For his dissections he, too, was roundly denounced by the clergy.

It was in this period of scientific awakening that modern obstetrics had its birth; when the untutored midwife, the priest-physician, and the barber sur-

*An address commemorating the Anniversary of the publication of the treatise by Semmelweis on puerperal fever, presented before The American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5, 1947.

geon gave way to men trained in the art of delivery. In their hands superstition, ignorance, and religious bigotry were the common clay out of which modern obstetrics was moulded.

William Harvey, called by Aveling the Father of British Midwifery in appreciation of his chapter on "Labour," was regarded by his envious colleagues as a crack brain. "They would not give a three-pence for his pills." After publishing his immortal work on the circulation of the blood, Harvey is quoted as saying: "I not only fear injury to myself from the envy of the few, but I tremble lest I have mankind as my enemy." The calumny heaped upon Harvey caused his practice to fall off and we find him loathe to publish his classic work, *Generation of Animals*, recalling the contentious reception of his immortal work on the circulation of the blood. "Much better," said he, "is it often times to grow wise at home and in private than by publishing what you have amassed with infinite pains to stir up unrest that may rob you of peace and quiet for the rest of your days." Harvey's most violent adversaries proved that eternal opposition could procure a certain kind of immortality.

For five generations the Chamberlain family was discredited and viciously attacked by the medical profession for withholding the secret of the "iron tongs." While deploring their secretiveness, it is only fair, as Aveling has said, to bear in mind that the Chamberlains lived at a time when it was common practice to withhold secrets of healing nostrums, when doctors in high repute extolled the virtues of mysterious healing potions.

Dr. John Burton, famed in Tristram Shandy for his foreeps, defied his critics with scathing sarcasm. In defiance of his adversaries he writes: "But for those people who like Birds of Night scream in the dark, when none can see them; and like cowardly enemies, unseen shoot their envenomed darts at me in secret whispers or anonymous papers, such creatures may split their malignant choler, till it consumes themselves, before I shall regard them in the least."

William Smellie had the indomitable Mrs. Nihell to contend with. Mrs. Nihell, of the hay market, was the doughty and uncompromising champion of a lost cause. Defending the midwife in her divine right to monopolize the practice of midwifery to the exclusion of the man midwife, Mrs. Nihell chose Smellie as her target whose forceps were "not so delicate as a woman's hands." If Smellie, "Master of British Midwifery," could be discredited, his murderous instrument would pass with him. Smellie suffered the usual hardships of a pioneer and crusader. In combatting the superstitions and vicious practices of the midwives of his time, he was subjected to the scurrilous attacks of those whose methods he condemned; attacks that did not end with the death of Smellie, but continued on for one hundred years.

In the sixteenth century Dr. Veitis of Hamburg, Germany, was condemned to the flames for attending a woman in labor; while in our own land, as late as 1754, Dr. James Lloyd of Boston was roundly denounced for immorality and licentiousness in a similar performance of his professional duties. But the calumny heaped upon him was as nothing compared to that meted out to James P. White as an aftermath of an obstetric clinic held at the University of Buffalo, New York, in 1850.

White was charged with the commission of acts of outrage against the rights of the community, against decency and propriety. He was libeled by the press and bitterly assailed by members of the medical profession. At the trial which followed it was contended that the exposure of the body of a parturient woman was wholly unnecessary to the successful conduct of the delivery; that to so expose a parturient woman to the vulgar gaze of the public is a "shock to the moral sensibility, diminishes the moral feeling, and debases the moral man." The vindication that ultimately came to Dr. White resulted in the establishment of the first obstetric teaching clinic in America.

Ephram McDowell, our American frontier surgeon of Danville, Kentucky, performed thirteen ovariectomies with eight recoveries at a time when anesthesia and antiseptics were unknown. His report of the first three operations appeared in 1817 and brought forth a storm of ridicule and skepticism. The veracity of McDowell was questioned by James Johnson, editor of the London *Medico-Chirurgical Review*, while others referred to the operation as brutal butchery and cruel. McDowell did not live to enjoy the fruits of his labors, a fate shared by many a benefactor of the human race. It was more than a century after his death that the profession fully realized that "pelvic and abdominal surgery began with ovariectomy, and ovariectomy began with Ephram McDowell, the backwood's surgeon."

William Hunter became the target of an outraged public opinion because of his anatomic dissections, as did William Shippen, Jr., America's pioneer anatomist and obstetrician. Shippen was berated and threatened with violence for exposing women in labor to the vulgar gaze of the midwives and doctors.

Sir James Y. Simpson was vigorously attacked by the medical profession that held to the age-old dictum that pain in labor is salutary and a conservative manifestation of life. He was excoriated by the clergy for defying the Almighty, for was not the pain of childbirth an ordinance of Divine Providence? Simpson will be remembered for his heroic efforts in overcoming all opposition to the relief of pain in childbirth. Let those who would pass ill-advised judgment upon the deeds of others mind the words of the discrete Simpson: "Obstetrics," said he, "is not one of the exact sciences, and in our penury of truth we ought to be accurate in our statements, generous in our doubts, tolerant in our convictions. Without these qualities science cannot be promoted nor truth educated." Patience, tact and perseverance were the secrets of Simpson's success. The contributions of Simpson and Semmelweis to obstetrics and surgery were made but a few weeks apart in the year 1847.

In the history of midwifery there is a dark page and it is headed *Semmelweis*. So wrote Fritch of Breslau. The page is dark because no man in the annals of medicine contributed more to the saving of lives and suffered more grievously at the hands of carping contemporaries. Semmelweis refused to be chained to the dogmas of a dead past, to the vagaries and the pedantry of the obstetricians of his time, and for his pains he was driven to the mad house. But with all this he has left a priceless heritage, and deserves well to be remembered on this, the one hundredth anniversary of his contribution to obstetrics.

“He was one of those mortals who was not always happy,” wrote Markhorsky, “but he was favored by fate, inasmuch as it was given to him to enrich science with a new idea and thereby to confer upon humanity an immeasurably important service.”

The name Semmelweis will ever be associated with that of puerperal sepsis, for it is to him, more than to any other individual, that credit is due for being the first to demonstrate through clinical and anatomical observations the etiology and the prophylaxis of the malady. The disease was not unknown to the earliest writers on medicine, to Hippocrates, Celsus, Avicenna, Pater, Sylvius, and Willis, but no mention was made by these authors of epidemics, nor does it appear that they were impressed with the seriousness of the malady.

The earliest reference to epidemic puerperal fever was made by M. Penu of Paris in 1646. He wrote of an epidemic that occurred in the Hotel Dieu of Paris in 1646 when scarcely a woman survived the disease. Later Pinard referred to an epidemic in the same institution in 1778 that took the lives of seven of twelve parturient women. Staff members counseled over what they called “the bothersome epidemic,” and out of their deliberations and their findings at the postmortem table the milk theory was evolved. From then on milk was banned from the hospital—but the epidemic swept on.

There were other theories evolved as epidemics swept through maternity wards in Dublin, Edinburgh, London, Vienna, Prague, Paris, and indeed throughout all continental Europe and Britain. There were the theories of overcrowding, of foul air, of errors in diet, of emotional influences, of gastric bilious fever, of inflammation of the pelvic organs and peritoneum, of miasma of the blood, of genus epidemicus, of lochial suppression, and atmospheric, telluric, cosmic influences. All these and more were the theories advanced by men eminent in the field of obstetrics as late as the middle of the nineteenth century. Out of all this hodge-podge and welter of theory and conjecture there was finally evolved a reasonable and tangible hypothesis that led to effective measures of prevention—this was the contribution of Charles White, Alexander Gordon, Oliver Wendell Holmes, and Semmelweis. They were the men who “traveled along unknown paths that later became open thoroughfares.”

Charles White of Manchester, England, almost a century before the time of Semmelweis, argued that childbed fever was a process of self-poisoning due to the absorption of the pent-up lochial secretions. As preventive measures he introduced the sitting posture to facilitate drainage, lime disinfection of the hands, clean linens, isolation of infected cases, and adequate ventilation of the wards of the Manchester Infirmary. And he boasted that under these restrictions not a death from puerperal sepsis occurred in his clinic.

That White anticipated antisepsis long before the time of Lister is evidenced by the following quotation from his *Treatise on the Management of Pregnant and Lying-in Women* (London, 1772): “I must not omit to mention in this place,” said he, “the good effects I have experienced from emollient or antiseptic injections into the uterus, by means of a large ivory syringe, or an elastic vegetable bottle—I have, by this means, known the fever much assuaged,

and, in many cases, wholly extinguished." White was first to recognize the entity of "milk leg"—later known as phlemasia albadolens.

Thomas Kirkland succeeded White in the Manchester Infirmary and made similar claims, as did Robert Collins in the Dublin Rotunda. So much from the British point of view on the mooted question of priority.

Why, then, we ask, did White fail to receive more generous recognition for his contribution to the solution of this vexed problem. The answer, in part, seems to be in the facts that White, unlike Semmelweis, lived in comparative obscurity far removed from the cross roads of medical progress. But more than all he did not possess the zeal of an evangelist—willing, if need be, to suffer martyrdom for a cause.

Closely following upon White came Alexander Gordon of Aberdeen, who in 1795 published *A Treatise on the Epidemic Puerperal Fever of Aberdeen* in which, for the first time, puerperal fever was proclaimed a contagion. Gordon's contribution was little noted on the Continent, so he escaped the defamation and the cynicism of his contemporaries in Europe; a misfortune that Semmelweis could not escape.

As Physician and Surgeon to the Infirmary of Aberdeen Gordon was in the thick of an epidemic of puerperal sepsis in the years 1790 to 1792. Twenty-eight of the seventy-seven patients died. Noting that these cases followed in the wake of certain doctors and midwives, he reasoned that some sort of contagion was carried from patient to patient by the attendants. Reasoning from clinical and postmortem observations, he arrived at the conviction that the disease was infectious. He counseled personal cleanliness on the part of the doctors and midwives and the fumigation of clothing and linens. It is to him that credit is due for being first to call attention to the contamination of wounds at the placental site—that puerperal fever is a wound contamination of the puerperal uterus.

"That the cause of this disease was a specific contagion or infection," said Gordon, "I have unquestionable proof—I had evident proofs of its infectious nature, and that the infection was as readily communicated as that of small pox or measles—I had evident proofs that every person who had been with a patient in the puerperal ward became charged with an atmosphere of infection, which was communicated to every pregnant woman who happened to come within its sphere. . . . These facts fully prove that the cause of the puerperal fever—was a special contagion or infection altogether unconnected with a noxious state of the atmosphere. Fresh air and cleanliness are insufficient for the destruction of contagion. There is no certain antidote but fire and smoke."

Gordon's influence with the populace was undermined by his insistence upon heroic purging and blood letting. He contended that he could abort the disease by such means if applied in full measure at the onset of the fever. "Hit hard and hit early," was his maxim. He contended that fumigation of the clothing and bedding and the washing of the hands of attendants were imperative, but, above all, the patient must be purged and bled to the limit of her endurance. Be it said to his credit he did abandon blood letting at the insistence of the populace, but continued on with the purging.

In our own country Oliver Wendell Holmes published a damning indictment against the medical profession in *The New England Quarterly Journal of Medicine and Surgery*. This was in April, 1843, four years before Semmelweis published his historic treatise on *The Cause, Concept and Prophylaxis of Puerperal Fever*.

Holmes' allegations were not based upon anatomic and clinical observations. He had little or no obstetric experience to back his assertions. His pronouncements were founded upon information that had come to him through personal correspondence and library research. Acting the role of a barrister pleading the cause of martyred mothers, the genial autocrat of the breakfast table declared: "The balance must be struck boldly and the results declared plainly. If I have been hasty, presumptuous, ill-informed, illogical; if my array of facts means nothing; if there is no reason for any caution in the view of these facts, let me be told so on such authority that I must believe it, and I will be silent henceforth, recognizing that my mind is in a state of disorganization. There is no quarrel here between men, but there is deadly incompatibility and exterminating warfare between doctrines. Let the men who hold opinions look to it, if there is any voluntary blindness, any interested oversight, any culpable negligence, even in such a matter, and the facts shall reach the public ear, the pestilence carrier of the lying-in chamber must look to God for pardon, for man will never forgive him."

The inimitable Holmes, academic physician and master rhetorician, gained undying fame here in the United States for his personal charm and matchless phrasing. But personality and faultless diction are no substitute for scientific research at the dissecting table and at the bedside. Holmes said puerperal sepsis could be prevented; Semmelweis proved that it could be.

Sir William Sinclair has this to say of the contribution of Holmes: "Here is the sum of the services of O. W. Holmes to obstetric science; as a science, it is a negligible quantity. But that Holmes conferred immense benefits on humanity by devoting his literary genius to attracting attention to puerperal fever and trying to suppress the practices which brought childbed fever in their train, is a fact which should be gratefully acknowledged.

But how, in the name of truth, does all this bring him into any sort of conflict or even comparison with Semmelweis? Still it brought down upon him the most truculent attacks from obstructionists in the highest official positions. Hodge, Professor of Obstetrics in the University of Pennsylvania, attacked Holmes with a certain amount of dignity not unworthy of the subject, but Meigs, Professor of Midwifery in Jefferson Medical College of Philadelphia, assumed the old aboriginal American style of warfare, and attacked him with a tomahawk and scalping knife of the Red Indian savage. He astutely hit the taste of his fellow countrymen, their gambling propensities, and their religious sentiments by attributing puerperal fever to 'chance or Providence.' "

While Holmes was making his passionate plea, Semmelweis was in the Allgemeines Krankenhaus in Vienna, battling with the scourge of puerperal sepsis, and all the while exerting all possible means of checking its ravages.

Ignaz Philipp Semmelweis was born in July, 1818, in the village of Ofen, a suburb of Budapest. He was the fourth of eight children; his father was a

shopkeeper. His early training was deficient, and all his life he was regarded by his critics as illiterate. After finishing grammar school in Ofen he enrolled in the University of Pest, and two years later he entered the Vienna School of Medicine where he remained one year and then returned for two more years to the University of Pest. His final year in medical school was spent in Vienna where he received his degree of Doctor of Medicine in April, 1844. In the following August he was granted the degree of Doctor of Midwifery.

July, 1846, found him in the First Lying-In Clinic of the Allgemeines Krankenhaus as First Assistant under Professor Klein. Referring to his first impression of the clinic Semmelweis said: "Everywhere questions arose, everything remained without explanation; all was doubt and difficulty. Only the great numbers of deaths was undoubted reality." It was here that he laid the foundation for the work that was to immortalize his name.

His daily routine consisted of caring for the patients in the ward and the instruction of students. In the early morning it was his habit to participate in autopsies, particularly on the bodies of women who had died of puerperal fever. The students also participated in the dissections; and, all the while, in the wards, in the dead house, and throughout sleepless nights, Semmelweis pondered over the tragedies enacted within his ward: "What is this fever?" "What is taking the lives of so many of my patients?" "How can it be prevented?" "How does it arise?" "What treatment can avail to halt the appalling death rate?" "Surely there must be something in the First Clinic that does not exist in the Second Clinic to account for the great discrepancy in the two wards. May it be that I and my students are the carriers of the contagion?"

While Semmelweis was brooding over his problem, an event occurred that ultimately gave to him the answer to the questions that had so long defied solution. Kolletschka, Assistant in Anatomy, received a stab wound in his finger while dissecting. Death resulted from the infection. Semmelweis witnessed the autopsy and saw the identical lesions which he had so often observed in the bodies of the women who had died in his ward of puerperal fever. He reasoned that Kolletschka had died of a wound contamination; that the contaminating substance was decomposed animal organic matter.

"Day and night, this picture of Kolletschka's disease pursued me," wrote Semmelweis in his *Etiology*, "and I was obliged to acknowledge the identity of the disease from which Kolletschka died with the disease of which I saw so many puerpera die. It was not the wound, but the contamination of the wound by cadaveric material that caused the death." It was this same substance that was being carried to his patients from the dead house to the lying-in ward—it was being carried there by himself and his students. "God only knows," said he, "how many women I have prematurely brought down into the grave!"

Determined to put an end to the scourge that was ravishing his ward, he gave orders that no students attending his ward could, at the same time, be in attendance on postmortem examinations; that before making examinations in his ward, the students must scrub their hands in a solution of chloride of lime.

Then the miracle happened. Within seven months the mortality from puerperal sepsis dropped from 11.4 per cent to 1.27 per cent. For the first time in

the history of the hospital the mortality was lower in the First Clinie than in the Second Clinie where only midwives were in attendance. In March and August of 1848 there was not a single death in the First Clinie.

The problem was solved to the satisfaction of Semmelweis, but it was quite another thing to convince his Chief and his colleagues and to have his Doctrine approved by the medical profession. This was the task he set himself to but, unhappily, it proved to be his undoing. Petty jealousies, stupidity, and willful blindness were to hinder his every effort. With few exceptions the obstetricians on the Continent, in Britain, and in the United States were committed to theories of their own, and would have nothing to do with the newfangled notions of the Hungarian Assistant.

Semmelweis had weighed their theories in the balance and found one and all wanting. He reasoned that atmospheric changes, overcrowding, faulty ventilation, and diet were not the answer, for these factors were identical in both the First and Second Clinics. Puerperal fever was not an epidemic, zymotic disease, like cholera and erysipelas, for such diseases show year-long intermissions, while puerperal fever is more or less constant. Inflammation of the pelvic organs and the peritoneum was not the cause, but rather the result of the contagion. And as for the milk theory, he did not trouble to affirm or deny.

Among his detractors was his Chief, Professor Klein, who, far from proferring encouragement and counsel, had placed every possible obstacle in his path, and finally demoted Semmelweis to the rank of Private Docent of Theoretic Midwifery, restricting his teaching to manikin demonstrations. No longer could he have access to the beds in his clinic.

Grieved and inconsolable, Semmelweis left Vienna without serving notice and returned to his beloved Budapest. But Budapest was not the city he had left in such high hopes to pursue the study of medicine. Hungary was in a state of revolution and, as with all things in Hungary, the medical profession, the University, and the St. Rochus Hospital were in a state of disorganization. Obstetric cases were admitted to the hospital only two months in the year. In the remaining months surgical cases occupied the lying-in ward. The surgeon-in-charge was also the coroner, and engaged in autopsies. Puerperal fever had, for years, been running rife in the hospital. In some months the mortality ran as high as 30 per cent. Semmelweis asked permission to take over the direction of the Lying-In Clinie in order that he might put an end to the scourge. And in May, 1851, he was placed in charge of the Obstetric Division of St. Rochus Hospital.

His first step was to sever all connection with the surgical department. The rules and regulations which he inaugurated in the Vienna Clinie were put in force and, as a result, the mortality from puerperal fever in his ward in the following five years fell to 0.85 per cent—an all-time low.

As Chief of the Lying-in Division of the St. Rochus Hospital, Professor Birly, like Professor Klein, in Vienna, would have nothing to do with the crazy notions of Semmelweis. Birly was a disciple of the *primæ viæ* theory and advocated the use of strong purgatives in the treatment of septic cases. To his

credit, Semmelweis made no issue with his Chief while quietly pursuing his course, trusting that in time his Doctrine would be accepted on its own merits.

Professor Birly died in 1855, and Semmelweis succeeded him as Professor of Theoretical and Practical Midwifery in the University of Pest. With the appointment came a rejuvenation of Semmelweis. Now, for the first time, he was his own master and was enjoying a measure of fame and the reward of a modest income from private practice.

But there were many handicaps and discouragements. The wards were too small to accommodate more than two hundred patients a year, yet it was always overcrowded and there was no provision for the isolation of infected cases. For the lack of an amphitheater, students received instructions while standing in the corridor. The hospital staff was unfriendly and disloyal. Regarding their Chief as a faddist and a crackpot, they were unwilling to carry out the preventive measures so essential to the success of the clinic. Yet, with all these handicaps, the mortality from puerperal sepsis in the years 1850 to 1856 remained at 0.85 per cent—an unheard of record for St. Rochus Hospital.

To this time Semmelweis had not appeared in print in support of his *Doctrine*. As a result there was much misunderstanding and conjecture as to the essential principles he was advocating. His friends were insistent that he resort to the printed word to put at rest the bickering and the willful misrepresentations that sprang from sources that could not be ignored.

Semmelweis finally yielded to the demands of his friends, and with resolute determination he set to the task of writing his *Etiology*. "My Doctrine," said he, "is either ignored or offensively assailed—indignation at the greatness of this scandal has thrust the pen into my unwilling hand; I think it would be criminal behavior on my part if I were longer to remain silent and neglect producing unbiased, impartial, and complete evidence in favor of the practical extension of my Doctrine."

For three years Semmelweis worked feverishly on his manuscript and in October, 1860, it was ready for the press. We, of our time, regard the work one of the epic-making contributions to medical literature. Not because of its literary qualities—for in this respect it was woefully lacking—but because of the fundamental principles laid down that have formed the basis for preventive medicine in the fields of obstetrics and surgery.

Much of the text was hurriedly assembled without regard for sequence and symmetry, thus leading to confusion. An endless array of statistics was incorporated in the text that few would care to wade through. Then, too, much of the text was devoted to acrimonious correspondence with the leading obstetricians of Europe. These letters were full of charges and countercharges, of censure and reflection, and to an extent that defeated the very purpose of his writing—that of winning converts to his Doctrine. The chapters devoted to "Etiology" and to "Prophylaxis" were brief and excellent. Had Semmelweis been content with these two chapters, leaving out much of the statistical material and all of the challenging correspondence, his work would have had a more favorable reception. But, being what it was, it was not well received. On the contrary, it only served to add fuel to the flame.

Enraged over the unfavorable reception of his *Etiology*, Semmelweis set to the task of writing *Open Letters to Sundry Professors of Obstetrics*. He would make one more effort to indoctrinate his traduceers in what he believed to be the only true nature of puerperal fever. "I shall do my utmost," said he, "to insure the cessation of murder, for anyone who dares disseminate the dangerous fallacies concerning puerperal fever will find in me an extremely active opponent. I am firmly convinced that there is no other way of putting a stop to those murders than the ruthless exposure of my adversaries, and no one whose heart is in the right place will blame me for the means I use."

From that moment to the day of his death Semmelweis engaged in an unremitting verbal combat with his critics, but the more he fanned the flame of calumny, the more he became involved in controversy.

"The controversy," said Waldheim, "became no longer a scientific encounter, no struggle to attain to a knowledge of the truth, but a thoroughly personal, hateful wrangling under the semblance of scientific discussion."

Wounded pride and deep resentment led Semmelweis into eriminations and personalities that served to alienate rather than to placate his opponents. Karl Schroeder regarded the Semmelweis Doctrine as one-sided and inadequate, and Max Boeler referred to the Open Letters, which Semmelweis addressed to sundry Professors, as extremely vehement and threatening. Josef Spaeth, while professing his conversion to the Semmelweis "Doctrine," expressed the opinion that his theory would have gained more obstetricians as open friends if he had not defended his theory in a tone which no man of science had been accustomed to up to this time. Carl Braun, Vischow, Zipfel, Siebold, Veit, Heeker, Seanzoni, and Denman were among his critics. Kiwish, of Wurzburg, would not be convinced, though in the year 1846 the mortality from puerperal fever in his ward was 26 per cent. Denman, of the Dublin Rotunda, said it would be a waste of time to dwell upon his Lehre. On the other hand Haller, Skoda, and Rokitansky of Vienna; Michaelis and Swarz of Kiel; Wiegner, of Strassburg; Kassmaul of Heidelberg, and Tilanus of Amsterdam, were among his supporters. Hebra rated the contribution of Semmelweis as comparable to that of Jenner. But even these men of high authority could not stem the tide of criticism. Hebra published a commendatory article in the *Journal of the Medical Society of Vienna* that was roundly criticized, and Skoda failed in having the Doctrine of Semmelweis investigated by the same society. Weigner, of Strassburg, endeavored to interest the French accoucheurs and failed, as did Arneth before the London Academy of Medicine. Everywhere Semmelweis was to feel the sting of professional intolerance.

Exasperated by the opposition, Semmelweis declared: "I have resolved to attack unsparingly all who dare to spread error regarding puerperal fever." To Professor Spaeth he wrote: "The Professor has given me the impression that his spirit has not been lighted up by the puerperal sun which arose in Vienna in 1847." And to Seanzoni of Wurzburg, then the leading obstetrician of Europe, Semmelweis wrote: "You have sent over all Germany a considerable contingent of practitioners who will, in their ignorance, engage in homicidal practice. I have formed an unshakable resolution to put an end to the mur-

derous work as far as lies in my power to do—I denounce you before God and the world as a murderer, and the history of puerperal fever will not do you an injustice when for the service of having been the first to oppose my teachings, it perpetuates your name as a medical Nero.” Such vitriolic expressions could hardly serve their intended purpose, that of winning converts to his “Doctrine.”

There came a time when the sensitive, impetuous nature of Semmelweis was unequal to the strain of violent controversy. In the early part of 1863 he began to have alternate attacks of excitability and melancholia; his memory failed him and his mind became clouded. He lost his professorship at St. Rochus, and in August, 1865, he was taken by his faithful friend, Professor Hebra, to an insane asylum in Vienna. There he died of a septic infection August 13, 1865, at the age of 47 years. The autopsy revealed a gangrenous wound in the finger of his right hand acquired in a surgical operation, lymphangitis in the right arm, metastasis in the eye, pyopneumothorax, and an extensive brain lesion. He died, as did his friend Kolletsehka, of the very disease he himself had sacrificed his life to conquer. May it not have been said of him as it was said of the Man of Galilee: “He saved others—Himself he cannot save.”

Appended to his Etiology, Semmelweis had written: “When I, with my present convictions, look back upon the past, I can only dispel the sadness which falls upon me by gazing into the happy future when within the lying-in hospitals, and also outside of them, throughout the whole world, only cases of self-infection will occur. But if it is not vouchsafed for me to look upon that happy time with my own eyes, from which misfortune my God preserve me, the conviction that such a time must inevitably sooner or later arrive will cheer my dying hour.”

Puerperal sepsis has not been wholly banished from the world as Semmelweis prophesied, but the principles laid down by him for its prevention have gone far in lessening the incidence of the malady. Semmelweis bequeathed to the modern maternity its supreme virtue—that of cleanliness. Furthermore, subsequent events have not altered the basic principles laid down by him on which the Doctrine of Semmelweis was founded. The contributions of Pasteur and Lister elucidated and confirmed his Doctrine.

His temporary burial was in Vienna, but later he was laid to rest in his native city of Budapest. In the garden of the Allgemeines Krankenhaus in Vienna is a marble slab erected to the memory of the most tragic figure in the history of medicine. And on the slab is a beautiful bronze tablet bearing the name *Semmelweis*.

In 1906 an international monument was erected in memory of the man to whom the world is indebted for his priceless contribution to humanity. There Semmelweis stands in full stature, holding a book under his arm and on the step of the pedestal sits a woman with her infant in her arms, her face upturned, gazing reverently at her benefactor.

The American Association of Obstetricians, Gynecologists, and Abdominal Surgeons revere the name of Semmelweis and unite with all obstetricians the world over in paying tribute to him on this the one hundredth year of his doctrine, and the eighty-second year of his passing.

WISE INDIFFERENCE OF THE WISE IN ANESTHESIA*

WESLEY BOURNE, M.D., MONTREAL, QUEBEC

ὥσπερ καὶ τὸ ἰατρεύειν καὶ τὸ ὑγιάζειν οὐ τὸ τέμνειν ἢ
μὴ τέμνειν ἢ φαρμακεύειν ἢ μὴ φαρμακεύειν ἐστίν; ἀλλὰ τὸ ὠδεῖ.**

Aristotle's Nicomachean Ethics,

Book V. ix. 16.

JOHN Dewey, "the most profound and understanding thinker on education that the world has yet known" (Ernest C. Moore), has said repeatedly that mankind so far has been ruled by things and by words, not by thought. Humanity has not been in possession of the conditions of secure and effective thinking. Unless we master things, we shall continue to be mastered by them; the magic that words cast upon things may indeed disguise our subjection or render us less dissatisfied with it, but after all science, not words, casts the only compelling spell upon things.

Ideas of this nature have been presented by other philosophers off and on throughout the ages. Indeed, they correspond to the meaning of the title of this paper, "wise indifference of the wise," which is taken from a line in Tennyson's poem, *A Dedication*. Strabo, the Greek historian and geographer, writing about the year A.D. 18, seems to have been impressed with the great importance which the Stoic philosophers attached to the virtue of "marvelling at nothing," when he said: "Writers also add the changes resulting from the migrations of peoples, wishing to develop in us, to a still greater extent, that virtue of not marvelling at things (a virtue which is lauded by Democritus and all the other philosophers; for they put it in a class with freedom from dread and from perturbability and from terror)," (*Geography*, 1, 3, 21). By heaping up instances of marvellous occurrences, he hoped to remove doubt and encourage the scientific spirit.

Cicero, in his *de Finibus Bonorum et Malorum*, says of the philosopher generally, "Even if he supposed happiness to consist in knowledge, still he designed that his study of natural philosophy should procure him peace of mind; since that is his conception of the Chief Good, which he entitles "freedom from alarm" (V. xxix. 87).

It would seem that these illustrations are, from our point of view, included in the sense of the epigraph of this address, taken from Aristotle, namely: "Just as to practise medicine and healing consists not in applying or not applying the knife, in using or not using medicines, but in doing so in a certain way." Elsewhere, Aristotle mentions the quality of high-mindedness as being pre-eminent and to be taken as embodying the trait most prized in an Athenian gentleman, a man "not easily moved to admiration, for nothing is great to him. He loves to possess beautiful things that bring no profit, rather than useful things that

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**"Just as to practice medicine and healing consists not in applying or not applying the knife, in using or not using medicines, but in doing so in a certain way."

—W. D. Ross, Oxford, London, 1925.

pay; for this is characteristic of the man whose resources are in himself. Further, the character of the high-minded man seems to require that his gait should be slow, his voice deep, his speech measured; for a man is not likely to be in a hurry when there are few things in which he is deeply interested, nor excited when he holds nothing to be of very great importance; and these are the causes of a high voice and rapid movements" (Ethics, IV, iii).

James Young Simpson wrote, in 1849, his book, called *Anaesthesia, or the Employment of Chloroform and Ether in Surgery, Midwifery, etc.* (Philadelphia: Lindsay & Blakiston): "The tyro looks at first upon the symptoms of an aggravated attack of hysteria as very serious. The physician of more experience knows they are not so. The stertorous breathing, the spasms, and almost convulsive symptoms, etc., sometimes produced by chloroform, may appear serious to those who have had little experience in the use of this agent. But everyone who has seen much of its effects knows that there is no danger following, but no inconvenience even left by such a show of serious symptoms." Coeval with Simpson, Dostoevsky told of one of *The Brothers Karamazou*, "that he was not proud of his fearlessness and seemed to be unaware that he was bold and courageous."

Numbers and numbers of other instances of *wise indifference* could be given, and, perhaps, particularly since one hundred years ago. Van Wyck Brooks (The World of Washington Irving) has written that "The forties were called in later times the 'mad,' the 'roaring,' the 'fabulous' forties, and this was indeed a singular decade in which, as Cooper said, the nation was passing 'from the gristle into the bone.' It was unique as a time of reforms and crazes, of Abolition and Fourierism, of 'esoteric anthropology,' of spiritualism, mesmerism, pathetism, phrenology, and what not. The nervous and mental interior turmoil implied in these various phrases—the battle-cries and banners of the forties—was matched by the turmoil of the outward life of this decade of 'Manifest Destiny,' the Mexican War, the Mormon trek, the settlement of Oregon. The most tumultuous years in the history of the country were those that led up to the climax of 1849; and yet their most notable aspect perhaps was this national mood of self-realization for which the American writers had prepared the way. . . . Already, in the early forties, there was an eager movement of mind in virtually every corner of the country. This was especially marked in New England, in Boston, in Cambridge, in Concord, but Charleston had its flowering too, the mind of Virginia was astir and Kentucky and Ohio were awake." Of such were the times when anesthesia became a reality.

Soon following, and seemingly antithetical somewhat to the theme of not marvelling, Walt Whitman wrote his *Miracles*:

Why, who makes much of a miracle?
As to me I know of nothing else but miracles,
Whether I walk the streets of Manhattan,
Or dart my sight over the roofs of houses toward the sky,

Or watch honeybees busy around the hive of a summer forenoon,
Or animals feeding in the fields,

These with the rest, one and all, are to me miracles,
The whole referring, yet each distinct and in its place.

To me the sea is a continual miracle,
The fishes that swim—the rocks—the motion of the waves—the
ships with men in them,
What stranger miracles are there?

LEAVES OF GRASS, VOL. II, 163.

All these thoughts may be summed up in the words of Sir Charles Sherrington, made not long ago in the *Gifford Lectures*, entitled, *Man on His Nature* (1937-1938), when in fancy he has Nature say to man: "Bethink you too that perhaps in knowing me you know the instrument of a Purpose, the tool of a Hand too large for your sight as now to compass. Try then to teach your sight to grow."

With reflections like these let us rejoice our poor hearts at this season of centenary celebrations concerning anesthesia; let us sing the praises of men like Long, Wells, Morton, and Simpson; and, without taking from these their glory, let us laud and magnify the good works of William Harvey, of Robert Hooke, of Robert Boyle, of John Mayow, of Joseph Priestley, of Antoine Laurent Lavoisier—le fondateur de la chimie moderne—, of Humphry Davy, of Michael Faraday, and of Henry Hill Hickman. In memory, let us do honor to all these men who gave hand in laying the foundation upon which was built the temple of anesthesia.

Last year in Boston there were meetings of dentists, of anesthetists, and of physicians and surgeons generally; all in commemoration of the hundredth anniversary of the first public demonstration of surgical anesthesia. Many papers were read, some belonging to the basic sciences, as these are related to anesthesia, and some dealing with the subject from the clinical point of view. An address, entitled, "*The Need for Wider Research*," was most brilliantly delivered by Raymond B. Fosdick. The audience was immeasurably moved by the seriousness of his remarks which were definitively provocative of thought for the future.

Not long after, the Association of Anesthetists of Great Britain and Ireland, in collaboration with the Royal Colleges of Physicians and Surgeons of England, held centenary celebrations in London. The outstanding features of this occasion were the unveiling of a plaque commemorating four British pioneers in anesthesia, namely, Henry Hill Hickman, James Young Simpson, John Snow, and Joseph Thomas Clover; and, the creation of *John Snow Medals*. These great gatherings, too, were elevating and brought to mind Samuel Johnson's *Inspiration*:

Breathing in the thinker's creed,
Pulsing in the hero's blood,
Nerving simplest thought and deed,
Freshening time with truth and good,

This year, 1947, marks an additional centennium in anesthesia, for it was one hundred years ago that James Young Simpson introduced the use of chloro-

form in obstetric practice in Edinburgh, although a little earlier in the same year, Pierre Jean Marie Flourens, the French physiologist, had shown "that the inhalation of chloroform caused in animals the same temporary type of anesthesia caused by the inhalation of ether."

Everybody knows of the heated controversy which followed the production of anesthesia in the parturient woman, and everybody knows that while in France Guizot, the scholar-statesman, was preparing the way for a general system of state-aided popular education, Lamartine was poet, historian, and orator; and while in America, Melville was writing *Moby Dick*, Simpson won the dispute by virtue of the acceptance of chloroform *à la reine*. It would seem that Herman Melville had thought as Simpson did think when he opened the eighty-first chapter of *Moby Dick* with the expression: "There are some enterprises in which a careful disorderliness is the true method." The thought is not unlike that of our title.

John Snow, the first physician to devote his full time to anesthesia, although he knew the dangers of chloroform better than anyone at that time, preferred to use chloroform. "His biographer, Benjamin Ward Richardson, tells the story that Snow was once challenged to give his reasons for thus persisting in its use if, as on his own showing it appeared, either were so much safer. He is said to have replied: 'I use chloroform for the same reason that you use phosphorus matches instead of the tinder box. An occasional risk never stands in the way of ready applicability.' " No doubt he was of the good opinion, which ought to be more general, that the best method is not necessarily the least dangerous, but rather that which offers an *optimum* for expediency.

Following the excellent investigative work of John Snow which lasted about ten years, progress in anesthesia was slow but, during the next half century, there were several valuable contributions, notably by Albert Niemann through the production of crystalline cocaine in 1860; by Edmund W. Andrews through the addition of oxygen to nitrous oxide for more prolonged anesthesia in 1868; by Claude Bernard, who, from his experimental studies, pointed out in 1875 that anesthesia, like other branches of medicine, should be based on physiological principles; by Paul Bert through his demonstration in 1878 that nitrous oxide anesthesia could be prolonged when this gas is mixed with oxygen and given under increased barometric pressure; by Carl Koller, who first used cocaine for "local" anesthesia in 1884; by Carl Ludwig Schleich through the production of infiltration anesthesia in 1892; by August Bier, who, in 1898, after producing true spinal anesthesia in lower animals, successively caused it to be carried out on himself, his assistant, Hildebrandt, and his patients; by Emil Fischer and J. von Mering through their inception of the barbiturates in 1903, while Woodrow Wilson was President of Princeton; by Alfred Einhorn in 1904, with his discovery of procaine; and by S. J. Meltzer and John Auer demonstrating the usefulness of intratracheal insufflation in 1909.

These are some of the examples of progress in anesthesia during times marred by misunderstanding. Then there came Frances Hoeffler McMechan who brought together the better elements concerning anesthesia. In no time,

those who were truly interested in anesthesia, the world about, regarded him as the single individual with talents which everyone shares. From this time on, many advancements have been made. Professor Dennis E. Jackson in 1915 described a method of removing the carbon dioxide of the expired air during anesthesia so that the same agents may be rebreathed with continually added oxygen in suitable proportions. Later, Ralph M. Waters developed this principle of eliminating carbon dioxide in clinical inhalation anesthesia. The year 1920 is famous for the development of intratracheal anesthesia by Ivan W. Magill, for the development of all forms of regional anesthesia by Gaston Labat, for the work of Arthur E. Guedel on the signs of anesthesia, and for the extending of epidural anesthesia by Fidel Pagés. In 1922 A. Goodman Levy published his excellent observations on chloroform. In 1923 ethylene was used to produce anesthesia by W. Esson Brown and by A. B. Luckhardt, J. B. Carter and Isabella Herb. Avertin was first used in anesthesia by O. Butzengeiger in 1926. The anesthetic properties of cyclopropane were demonstrated experimentally in 1928 by C. H. W. Lucas and V. E. Henderson, and this drug was used in man by Ralph M. Waters in 1930. In the same year, Chauncey D. Leake and M. Y. Chen brought forward divinyl ether. Evipan, a barbiturate, was given intravenously to produce anesthesia by H. Weese and W. Scharpff in 1932. Another short-acting barbituric acid derivative, pentothal, was introduced by John S. Lundy for intravenous anesthesia in 1934. The "continuous" method of spinal anesthesia was presented to the profession in 1940 by W. T. Lemmon. Harold Griffith initiated the employment of curare in anesthesia in 1942.

These are some of the recent innovations, *pari passu*, with which there have been several very particularly important improvements in anesthetic appliances made in England and in the United States, especially by Charles King, by Karl Connell, by E. I. McKesson, by R. von Foregger, and by J. A. Heidbrink. Simultaneously, too, there have been numerous publications dealing with the problems of anesthesia, many of them highly scientific and disclosing the results of the efforts of distinguished investigators.

These energetic men of wisdom, while indulging that lively element of thought, imagination, have been wisely indifferent of mystery and from their works have explained, in large part, some effects of the drugs used in anesthesia upon the vital processes which belong to the nervous system, to respiration, to the circulation of the blood. For example: J. H. Quastel (1939), from his studies on the high rate of oxygen consumption in the brain, has suggested that an anesthetic hinders the cells of a nervous center from oxidizing pyruvic acid, lactic acid, and dextrose; M. Jowett (1938) has shown that a definite inhibition of respiration is caused by anesthetic concentrations sufficient to produce narcosis, and suggests that the interference of dextrose oxidation may account for anesthesia; and some others have demonstrated that in high spinal anesthesia breathing is depressed, the heart is slowed, blood pressure is lowered, and red cells leave the circulation, these four factors seriously affecting tissue metabolism. Another example is the histotoxic action which many of the drugs used in anesthesia are capable of producing. It becomes manifest by acidosis and such

functional derangements as may be seen in the liver and elsewhere. Thus allured ineludibly, indeed ineluctably, we find ourselves following an illimitable course crossed, it is true, by many a bourne but with never-finishng frontiers, over each of which the beacons of those beyond become more and more beckoning as one by one measures are made sure. He who would go this way, in the language of Tolstoy, must eschew the only two sources of human vice, idleness, and superstition, and pursue the only two virtues, activity and intelligence.

At any stopping point one may see many ways from which to choose among the Jeffersonian. More particularly, an anesthetist now-a-days is bound to consider the functional activity of the capillary bed as it is being looked into by Robert Chambers and B. W. Zweifach; he must be familiar with capillary permeability as regarded by Eugene M. Landis, and with the relation between intercellular substance and tissue growth now being shown by Eliot R. Clark; he must follow the course of protein outside the vessel and in the lymphatic system, which is being studied by Cecil K. Drinker; it becomes his duty to watch with William E. Ehrlich the function of the lymphocyte; and, seeing that the problems in nutrition as regards proteins, their hydrolysates and proteases are of such general importance, it is necessitous for him to know the works of James B. Allison, John P. Peters, Robert Elman, and G. H. Whipple. Good reference to the publications concerning studies like these is given in the *Annals of the New York Academy of Sciences* of last year.

But these are not all of the cynosures of the anesthetist, for beyond even the fundamentals of oxidation and respiration (L. Michaelis), there are those matters of education, the general principles of which pervade the thoughts of our leaders, James B. Conant, and Sir Richard Livingstone, for examples. Increasingly our universities are supporting more prolonged postgraduate courses in anesthesia.

Inexorably the investigator flags not nor swerves from the path of discovery, while he does not allow himself to marvel immoderately. He will keep in mind the advice of Horace:

.
Nil admirari prope res est una, Numici,
solaque quae possit facere et servare beatum.
Hunc solem et stellas et decedentia certis
tempora momentis sunt qui formidine nulla
imbuti spectent.

.
Vive, vale. Siquid novisti rectius istis,
candidus imperti; si non, his utere mecum.

EPISTLE VI.

Translation:

"To wonder at nothing is about the one and only thing, Numicius, which can make a man happy, and keep him so. This sun and stars and seasons which depart at regular periods, some there are who view, not infected with any dread: . . . Live long, farewell; if aught you know more true than these precepts which you read, frankly impart them to me; if not, like me, use these."

James Lonsdale and Samuel Lee, Macmillan & Co., 1908.

SINGLE INJECTION CAUDAL FOR OBSTETRICAL ANALGESIA AND THE USE OF PONTOCAINE

WILLIS E. BROWN, M.D., F.A.C.S., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa)

CAUDAL anesthesia is reported¹ to have been first described by Cathelin in 1901, and adapted to obstetric procedures by Stoeckel in 1909. Since then many workers² have employed it, but its usefulness was limited almost entirely to the perineal phase of labor and delivery, since only a single injection was given. In this phase of parturition other agents were more effective, so that local and caudal anesthesia in obstetrics made little progress. In 1939, Lemmon^{2a} reported a "continuous spinal technique by which the duration of anesthesia from intraspinal injections could be prolonged more or less indefinitely." Hingson and Edwards^{2b} modified this technique to provide continuous caudal anesthesia. This method employed a malleable needle placed in the caudal canal so that frequent intermittent injections of short acting local anesthetic agents could maintain anesthesia for many hours.

This method achieved brief popularity and still offers much to the patient in labor. As would be expected, many difficulties were encountered, and studies have been continued to improve on this basic principle. The chief problems encountered in continuous caudal anesthesia included neurological changes induced by the needle, dislodgment of the needle, necessity of constant attendance of a physician, and technical difficulty in placing the malleable needle. It was decided to make a clinical study in which the anesthesia was prolonged by the use of long acting drugs instead of by an indwelling device. This paper reports our observations on a single injection caudal technique.

The experience of Brown⁴ and others⁵ suggested that pontocaine in normal saline solution would be satisfactory for clinical use. The fixation of this agent in the nerves of the caudal canal was augmented by the addition of adrenalin. A 22 gauge Pitkin needle was selected because of its flexibility, small size, and ease of handling. It can be introduced without a local anesthetic wheal which obscures the caudal hiatus. It was technically much easier to place than the malleable needle or the catheter. The first observations were made using 30 c.c. of 0.1 per cent pontocaine solution in 0.9 per cent NaCl solution with added adrenalin.

Several difficulties were promptly encountered. The level of the cutaneous anesthesia varied from just above the symphysis to above the umbilicus. It was also noted that cutaneous anesthesia to the umbilicus was not uniformly associated with relief from the pain of uterine contractions. Because of these factors many of the patients obtained only partial relief from uterine pain. It was impossible to confirm the observations of Hingson and Lull¹ that uniformly satisfactory analgesia can be obtained with levels of cutaneous anesthesia between the symphysis and umbilicus. Fifteen to twenty per cent of the patients will suffer uterine pain even with cutaneous anesthesia at the umbilicus. It seems rather that consistent relief of the abdominal pain of uterine contractions requires cutaneous anesthesia nearly to the costal margin.

In an attempt to increase the duration and effectiveness of the anesthesia, similar amounts of a more concentrated pontocaine solution (0.2 per cent) were

employed. These frequently failed either because the level of anesthesia was insufficiently high to produce satisfactory analgesia or the amount of pontocaine induced toxic reactions.

A survey of these data suggested that the volume of the caudal canal varied widely, and that the incidence of toxic reactions from pontocaine introduced into the caudal space increased rapidly when the dose exceeded 40 mg. (Figs. 1 and 2). Satisfactory clinical results apparently depended on placing an adequate but subtoxic amount of drug in a volume of diluent sufficient to fill the epidural space up to the eighth or sixth thoracic segment.

Two factors might conceivably influence the level of anesthesia obtained from any given volume of injected anesthetic solution: the rate of injection and the capacity of the epidural space up to the desired level. Since the rate of injection was relatively constant (as rapidly as the solution could be injected through a No. 22 needle, about 1 to 2 c.c./second), it seemed probable that the height of anesthesia was a function of the volume of injected material. Thus it became apparent that for a single injection technique to be effective some method of estimating the volume of the epidural space to the required level was necessary.

At this point, it was decided to estimate the capacity of the epidural space by using a fixed volume of a relatively nontoxic agent such as procaine. Depending upon the results obtained, one could then inject pontocaine solution in appropriate volume and concentration to obtain an adequate level of anesthesia for any given patient. Thirty cubic centimeters were selected, since this is the most commonly suggested volume for adequate anesthesia. By determining the height of anesthesia obtained with 30 c.c. of procaine solution the volume necessary to obtain cutaneous anesthesia between the umbilicus and costal margin could be estimated.

Technique

The following technique was developed: the analgesia is begun when the patient is definitely in labor and complaining of pain, provided no contraindications to caudal injection are present.

1. Under aseptic conditions a 22 gauge Pitkin needle is introduced directly into the caudal space, the patient lying on her side.

2. Due precautions are taken to ascertain that the needle is not in the intrathecal space or in a blood vessel.

3. Thirty cubic centimeters of 1 per cent procaine solution are injected moderately rapidly (1 to 2 c.c. per second). This injection permits the anesthetist to determine clinically by standard signs and symptoms that the needle is in the proper space. It also permits the clinical estimation of the volume of the caudal canal and epidural space by determining the level of the anesthesia obtained with this volume. The needle is left in place during the ten to fifteen minutes necessary for the level of the anesthesia to be developed.

4. Thirty to 40 mg. of pontocaine are prepared in a volume of saline solution estimated from the height of anesthesia obtained with 30 c.c. of procaine.*

*For example, if 30 c.c. of procaine solution produces anesthesia to the level of the umbilicus, the volume of pontocaine solution should not exceed 35 c.c. On the other hand, if 30 c.c. of procaine solution produces anesthesia only to the symphysis, 40 to 50 c.c. would be necessary to obtain adequate obstetric analgesia. No fixed concentration of pontocaine is used; rather 30 to 40 mg. of pontocaine is dissolved in 30 to 50 c.c. of saline, producing a 0.1 per cent to 0.05 per cent solution.

5. Ten to fifteen drops of 1:1,000 adrenalin are added and the pontocaine solution injected moderately rapidly (1 to 2 c.e. per second).

6. The needle is withdrawn and the patient turned on her back or on the opposite side according to clinical indications.

7. If the membranes are intact, they are ruptured providing there is no obstetrical contraindication, and the patient is returned to her bed.

TOXIC REACTIONS

Mgm. Pontocaine Causing Reaction

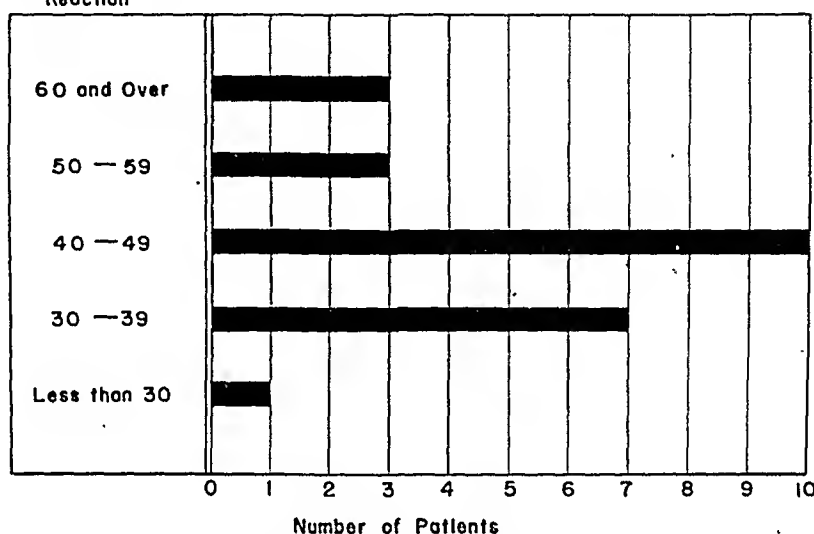


Fig. 1.—The incidence of toxic reactions correlated with the amount of pontocaine injected. There were twenty-four patients with reaction at some time during their analgesia; often the reaction occurred with only one of two to three injections.

VOLUME OF ANESTHETIC SOLUTION AS SINGLE INJECTION NECESSARY FOR SATISFACTORY ANALGESIA

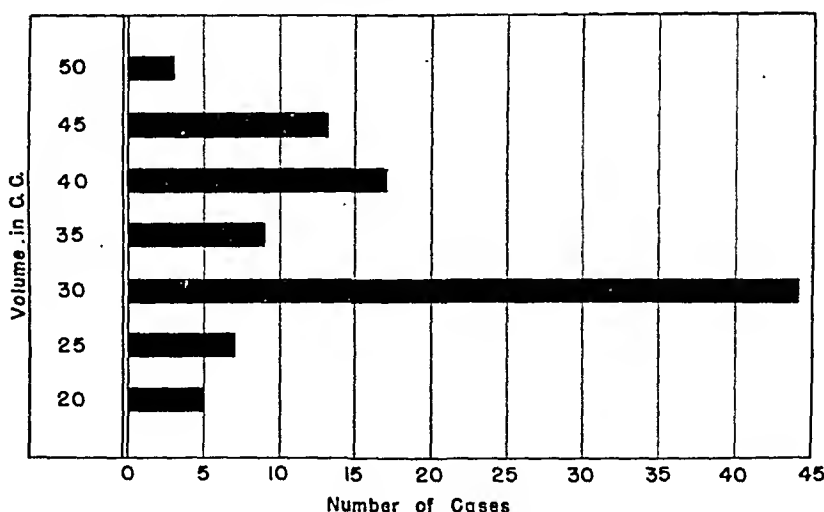


Fig. 2.—Total cases, 98; with adequate record. If 30 c.c. are selected, 12 per cent would receive an overdose and 33 per cent an inadequate amount. If 35 or 40 c.c. are selected, it is to be presumed that some of the patients with a small volume epidural space would have had excessively high anesthesia; also with this volume of medication, 16 per cent of the patients would not have had satisfactory analgesia for labor (uterine contraction pain).

TABLE I. GENERAL DATA

	NO. CASES	1ST STAGE	2ND STAGE	3RD STAGE	OUTLET FORCEPS WITHOUT ROTATION	OTHERS WITH OPERA- TION*	SPON- TANEOUS DELIVERY	ASPHYXIA MILD MOD.	FETAL DEATHS
Primipara	43	14h18'	1h37'	7'	30	2	11	4 1	21
Multipara	63	9h28'	44'	5'	24	5	34	1	0
Total	106				54/50%	7/7%	45/42%		

*Breech extraction—midforceps, low forceps with rotation—twins, etc.

†One child premature weighed 1,035 grams. One child—macerated stillborn.

Data

One hundred forty-eight patients have been studied. The usual obstetric data are presented in Table I. Of these, 106 had completely satisfactory anesthesia, or nearly so, and 42 were partial or complete failures. Most of the complete failures were due to technical difficulties, while the partial failures were usually attributable to insufficient volume of anesthetic solution (Table II).

TABLE II. REASON FOR FAILURE

	NO. CASES
Technical and anatomic causes	31
Time too short	7
Severe toxic reactions	1
Only partial relief	2
Uncooperative patient	1
Total cases	42
Successful 72%*	

*This includes attempts by house staff and interns and the earlier experience of the study. The personal experience of the author approximates 85 per cent successful.

The duration of the analgesia ranged from six hours to forty-five minutes and decreased with succeeding injections of pontocaine. There is no good explanation for this phenomenon. Clinically, the average duration of analgesia with the first injection was three and one-half hours, while the average of the second and third injections was two and three-fourths hours, and the average of the fourth injection one and one-half hours (Table III).

Despite the fact that the level of the anesthesia was carried somewhat higher than has been previously recommended, vasomotor reactions were minimal. They are tabulated in Fig. 2 and Table IV. Changes in pulse and respiration were not significant. With one exception toxic reactions were mild. Significant depressions of blood pressure occurred in five patients. (Table IV.) One of these (R. N.) occurred after the use of a 0.2 per cent pontocaine solution and was probably due to a toxic reaction rather than to a vascular change. This patient received 75 mg. of pontocaine in an attempt to raise the level of anesthesia. Barbiturates and oxygen therapy were employed: convulsions or unconsciousness did not develop. Labor progressed during this reaction and delivery occurred satisfactorily before the analgesia wore off.

The majority of these patients were delivered by outlet forceps (Table I) because of the lack of a bearing down reflex. In some patients the caudal analgesia was permitted to wear off in the belief that as it receded the bearing down reflex would be restored and spontaneous delivery would occur. This was not the case, for the anesthesia receded segmentally from above downward. As the anesthesia wore off the patients suffered uterine pain prior to the return of the perineal reflex. With the loss of the coordinating influence of the bearing down

reflex the patients became uncooperative and it was necessary to introduce an inhalation anesthetic agent for delivery. It was also observed that as the caudal anesthesia wore off many patients suffered abdominal pain from uterine contractions but still had sufficient pelvic and perineal anesthesia to permit episiotomy, forceps delivery, and repair without additional anesthesia.

TABLE III. DURATION OF ANALGESIA

		AVERAGE DURATION OF ANALGESIA
First injection		3 hours 19 minutes
Second injection		2 hours 42 minutes
Third injection		2 hours 59 minutes
Fourth injection		1 hour 21 minutes
Range	Longest*	6 hours 10 minutes
	Shortest	45 minutes

This is the average duration of each injection in patients who had more than one injection, or in whom the anesthesia was permitted to wear off.

*One patient had severe toxic reaction from 75 mg. pontocaine and her analgesia lasted 7 hours and 10 minutes.

TABLE IV. TOXIC AND VASOMOTOR REACTIONS

PATIENT	TYPE OF REACTION
P. C.	Blood pressure 76/40 for ten minutes
P. S.	Nausea and emesis, once
M. H.	Nausea and emesis, once on second injection
R. W.	Nausea and emesis on fourth injection
E. L.	Nausea and emesis, slight with first injection
B. H.	Slight nausea
V. R.	Nausea and emesis, once
N. G.	Nausea and emesis
F. N.	Nausea and emesis, once
H. G.	Nausea and emesis
D. B.	Emesis, two times
T. P.	Nausea and emesis
M. S.	Nausea
C. L.	Nausea and emesis
L. H.	Nausea and emesis, two times, B.P. 80/40
O. H.	Nausea and emesis
E. M.	Headache
E. G.	Headache
H. C.	Dyspnea, B.P. 70/30
V. B.	Nausea and headache
R. N.	Nausea, cyanosis, emesis, headache, B.P. 60/40
A. W.	Nausea, headache, B.P. 66/40
B. B.	Nausea, B.P. 90/40
D. B.	Nausea and emesis

Blood loss under caudal analgesia is reduced. This observation has been reported by others and is confirmed by this series. Despite the fact that many of these deliveries were managed by students and residents, the average blood loss for primiparas was 186 c.c. and for multiparas 133 c.c. or an average of 145 c.c. Only twenty-one patients had a blood loss of 200 c.c. or over (Fig. 3).

Perhaps the greatest single advantage of caudal analgesia and anesthesia in obstetrics is obtained for the baby. There was no significant asphyxia in the infants who were delivered under caudal anesthesia alone. All infants cried spontaneously following the clearing of the airways and/or gentle skin friction. Of the children whose mothers required inhalation agents as an additional anesthetic for delivery (using the caudal for analgesia), one required stimulation with contrast baths and oxygen; none were severely asphyxiated. There were two fetal deaths. One was a premature infant weighing 1,035 Gm. and the other a macerated stillborn child (Table I).

BLOOD LOST

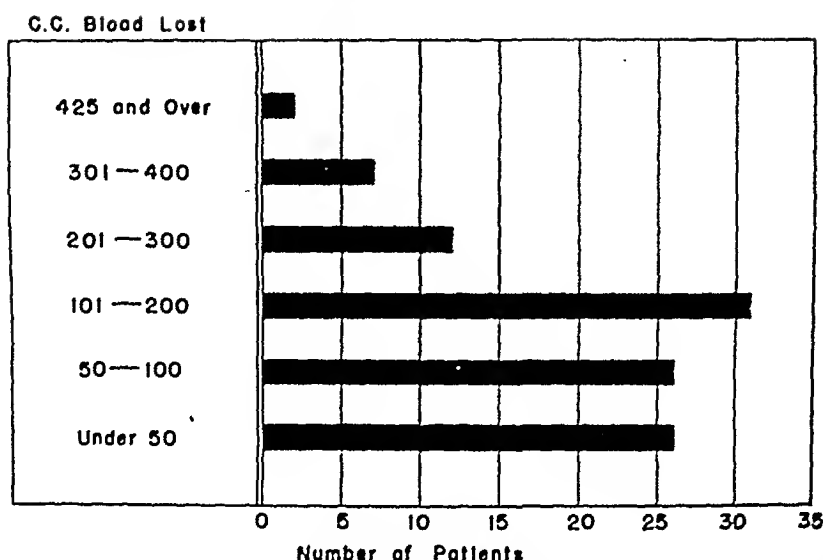


Fig. 3.—Blood loss in patients delivered under caudal analgesia and anesthesia. The blood loss is recorded as measured and/or estimated. The sum of these two is the total recorded blood loss. Average 145 cubic centimeters.

Discussion

These observations confirm those of other investigators on caudal analgesia. Single injection caudal like continuous caudal anesthesia modifies all three stages of labor. The mechanism of this altered physiology has not been determined. The first stage is shortened appreciably. The second stage of labor is prolonged depending on the duration of the anesthesia. No precipitate or unattended births occur; as long as the anesthesia is adequate, the patient comfortably waits for the obstetrician. The third stage is considerably shortened and the blood loss is minimal. The puerperium is unaffected. In this series a few patients required catheterization during the first twenty-four hours post partum. There were no neurological complications.

In addition, there are certain other clinical advantages of the single injection method which should be mentioned. Caudal analgesia offers much to the woman in labor and has many advantages to her child. However, the technical problems, the complications, and the amount of time required of the physician by multiple injection techniques have greatly reduced its use.

The use of the small gauge flexible needle, instead of the larger caliber malleable needle or trocar and catheter, greatly facilitates the proper placing of the needle. The smaller needle obviates the necessity of a local wheal which often obscures the hiatus, and the stiffer needle makes introduction much easier.

The estimation of the volume of the caudal and epidural space permits fairly accurate individualization of the volume of the injected drug, and thus insures more satisfactory clinical results and fewer toxic reactions.

This technique permits the use of the more toxic but longer acting drugs which produce three to five hours of anesthesia from a single injection. Any toxic or vasomotor reactions occur within the first ten to fifteen minutes following the injection. The physician may then safely leave his patient to the care

of a nurse for several hours. This freedom has obvious advantages in private practice.

Lest one feel this is a panacea for the problem of obstetric analgesia and anesthesia, a word of caution is in order. The same problems, complications, and risks inherent in continuous caudal analgesia must be considered with this method. The same safeguards for the injection of local anesthetic drugs and for caudal anesthesia must be observed with this method. They have been re-cited in other publications and are not repeated.

Nevertheless, with reasonable safety, one can largely obtain the following four freedoms of obstetrics:

1. Freedom from labor pains
2. Freedom from fetal asphyxia
3. Freedom from the risks of the inlying needle or catheter
4. Freedom from constant physician attendance

Summary

1. This report details observations on single injection pontocaine caudal anesthesia in labor and delivery.

2. A technique is described by which the volume of the caudal and epidural space can be estimated by injecting 1 per cent procaine solution thus permitting the injection of the proper amount of pontocaine solution.

3. Analgesia lasting from three to five hours may be obtained by single injections of pontocaine solution.

4. The relief of pain during labor and delivery is satisfactory when adequate levels of anesthesia are obtained.

5. This single injection technique is clinically easier than the continuous methods.

Acknowledgment is gratefully made to Dr. Stuart Cullen for his suggestions and help. The pontocaine solution used was generously supplied by Winthrop Chemical Company.

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Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Cantone, C.: Early Primary Carcinoma of the Isthmus, *La Ginecologia* 12: 331, 1946.

Cantone reviews the literature on primary carcinoma of the isthmus, and mentions the opinion of some authors doubting the very existence of the isthmic carcinoma as a separate entity, and relates a case of his own observation, in which the lesion was no more than a pinpoint ulceration, in the center of the isthmus, so that no doubt could arise of its primary place of origin.

GEMMA BARZILAI.

Curran, John F., and Kilroy, Edward A.: Coexistent Primary Carcinoma of the Fallopian Tube and of the Breast, *New England J. Med.* 236: 64, 1947.

The authors report a patient on whom a supravaginal hysterectomy and left salpingo-oöphorectomy was performed. At the same operation a breast tumor was removed. Ten days later a radical mastectomy was performed.

The left tube proved to be a primary carcinoma, and the breast tumor was a primary medullary carcinoma. X-ray or radium therapy was not given the patient postoperatively.

A few of the more important considerations regarding the incidence, diagnosis, and treatment of primary carcinoma of the Fallopian tube are discussed.

JAMES P. MARR.

Barigozzi, C., and Cusmano, L.: Studies on Chromosomes in Human Cancer Cells, *Bollettino Della Societa Italiana Di Biologia Sperimentale* 22: 1, 1946.

In a study of six cases of basal cell carcinoma of the cervix, Barigozzi and Cusmano demonstrated mitotic figures in which a peculiar aspect of chromosomes is present, that may be quite significant.

The material was prepared according to Barigozzi's technique for demonstration of chromosomes (fixation in alcohol-acetic acid, crushing and dyeing with neutral red).

Mitotic figures were seen with 24 chromosomes with evident longitudinal ridge, undergoing a metaphasic stage, similar to a reduction phase in a meiosis. In others, a prophase corresponding to a pachitenic phase was evident. In still others, showing a prometaphase stage, terminal chiasma were absent, and reduction to an aploid number of chromosomes was the end-result. The reduction of an ordinary diploid nucleus to an aploid one has not been observed as yet in human body cells. This finding bears some analogy to Evans and Svezey and Hearn's statements, and to what has been observed in mice cells cultivated in vitro and treated with carcinogenic hydrocarburates.

GEMMA BARZILAI.

Endocrinology

Leatham, James H.: Further Studies on Antigonalotropin Formation Following Gonadotrophic Hormone Administration, *Am. J. Physiol.* 148: 700-707, 1947.

Leatham ascertained experimentally that antigonalotropin formation against a combination of sheep anterior pituitary extract and human chorionic gonadotropin ("Synapoidin") could be induced more rapidly in the rabbit by subcutaneous than by the

intravenous route of administration. These inhibitory substances disappeared within twenty to forty days. Animals given a reinjection series demonstrated that antigonadotropins formed more readily and persisted for a greater length of time forming hormone administration in a reinjection series.

The author also observed that, despite the reduction in gonadotrophic potency induced by standing at room temperature, there was indicated no evidence of a decrease in ability to elicit antihormone formation.

The antigonadotropins were shown to possess a nonspecific nature by the ability of serum to nullify the gonadotrophic action of pregnant mare serum and human chorionic gonadotropin in the male and female rat. Furthermore, human pituitary and male rat pituitary extracts were antagonized in the female rat, but the male rat pituitary solution was not inhibited in the male test animal. Gonadotrophic extracts of reduced potency through aging process elicited a nonspecific inhibitory serum from injected rabbits.

The writer found a pronounced inhibitory effect on the reproductive system of male mice following the administration of the antigonadotrophic serum. There was atrophy of the gonads and castration-like changes in the pituitary gland. The testes of serum-treated mice averaged only 24 Gm. and were devoid of spermatozoa, whereas the testes from the controls averaged 99 Gm. and all exhibited spermatozoa. The seminal vesicles too reflected the effect of antigonadotrophic serum; the treated series averaged 7 mg. each compared to 26 mg. in the control group. Furthermore, the adrenal X-zone which normally disappears with the maturation of the male reproductive system and was absent in the controls was found to be present in the serum-treated mice, a further indication that androgen was not being excreted.

C. E. FOLSOME.

Sammartino, R., and Blanchard, O.: Placental Changes in the Rabbit and Abortion Induced by Estrogens, *Obst. y Ginec. Latino-Am.* 4: 533-549, 1946.

The authors studied the placental changes which occur in rabbits after the parenteral injection of estrogens. The latter brought about fetal death and expulsion from the uterus in the second half of pregnancy on the fifth, sixth, and seventh day following a single injection of estrogen. Larger amounts of estrogen were given and over varying periods of time, and the uteri and placentas were studied. It was found that when the injection of estrogen produces an abortion it does so by altering the maternal circulation which seems to exert a pathologic effect directly on the fetal ectoderm. No disturbances were observed in the corpus luteum.

J. P. GREENHILL.

de Santiago, A. P.: Implantation of Pellets of Progesterone, *An. brasil de ginec.* 21: 434-439, 1946.

The author implanted pellets of progesterone into four patients. Three of the patients suffered from menometrorrhagia of puberty, and the fourth had a threatened abortion. The pellets contained from 50 to 100 mg. of progesterone, and implantation was early performed under direct infiltration anesthesia. In one patient an aseptic suppurative process occurred, and the remains of the pellet were expelled. This occurred after the uterine bleeding had stopped. The author believes that the body treated the pellet as a foreign body which was no longer needed. The results in all the cases were satisfactory.

J. P. GREENHILL.

Gynecology

Casabona, Umberto: Tuberculosis of Cervix, *La Ginecologia* 12: 2, 1946.

Casabona describes a case of tuberculosis involving a small district of the cervical canal solely, between the internal and external os. This extremely rare intracervical localization of the disease has formerly been described by Pestalozza, Cova, Kaufmann, Alfieri, and Brouha, and signs and symptoms thoroughly discussed.

The main interest arises from the fact that the disease is easily overlooked, and furthermore easily mistaken for carcinoma when discovered.

In Casabona's case, early and correct diagnosis was made because of the association of a primary tuberculosis of the lung, and secondary amenorrhea of two years' duration in a 31-year-old woman, and the presence of a sticky, mucopurulent vaginal discharge containing Koch's bacilli.

The lesion was of finely branching papillary type, the covering epithelium recalled the tall cervical type, while in others, cells appeared swollen, filled with an opaque secretion product quite different from normal mucus. Cervical glands looked fairly normal, except for exudate in lumen and dilation. The connective tissue stalks contained giant cells and lymphocytic infiltration. After the surgical ablation of the diseased area of the cervix, menstrual flows reappeared, the discharge stopped, and Koch's bacilli were not found again. A survey of theories related to formal pathogenesis of amenorrhea in early and circumscribed tuberculosis of the genital tract is given.

GEMMA BARZILAR.

Guerriero, William F., Jennett, R., and Mantooth, W. B.: Infectious Granulomatous Lesions of the Cervix, J. A. M. A. 133: 832, 1947.

The authors classify the infectious granulomas of the cervix as those resulting from tuberculosis, granuloma inguinale, syphilis, and chaneroid. Their clinical importance depends upon their differentiation from carcinoma. In about 85 per cent of the cases tuberculosis of the cervix is secondary to disease of the Fallopian tubes, lungs, genitourinary and gastrointestinal tracts. The various pathologic types of ulcerative, miliary, papillary, and bacillary catarrhal are described. Leucorrhea and bleeding are prominent symptoms. Generalized systemic symptoms may also be present. Treatment may be curative or palliative.

Like tuberculosis, granuloma venereum cervicitis will be found with correct diagnosis to be a relatively common lesion, particularly in the Negro. It is frequently difficult to differentiate from carcinoma, and the lesions may extend to the adjacent tissues. The diagnosis depends upon the finding of Donovan bodies in the smear or scrapings or biopsy. The diagnosis is not a simple matter. Therapy is general, local, and specific. General therapy consists of adequate diet, penicillin, and sulfonamide compounds. Local therapy in the form of sulfonamide jellies may be of benefit. Specific therapy consists of the administration of antimony compounds over a period of six months. Special complications may result when the disease occurs during pregnancy.

Cervical syphilis may be primary, secondary or tertiary. Chancre of the cervix does not present the same clinical manifestations as a similar lesion of the outer genitals. Microscopically the biopsy represents a picture of chronic inflammation and only the finding of *spirochaeta pallida* by dark-field examination in early lesions will substantiate the diagnosis. In late lesions the diagnosis is made by positive serology and biopsy.

Chaneroid of the cervix is rare. It is caused by the gram-negative, *Hemophilus ducreyi*. Diagnosis is made by smear culture, skin test, and biopsy. The smear is the conclusive method of diagnosis and positive culture are effective only in about 40 per cent of the cases. Treatment consists of the administration of sulfathiazole parenterally and locally for seven to ten days.

WILLIAM BERMAN.

Gynecologic Operations

Stearns, Howard C.: A Report on Experience With Vaginal Hysterectomy, West. J. Surg. 55: 220, 1947.

The author relates his experience with vaginal hysterectomy. He feels that the operation has never been given its rightful place in American Gynecology. In considering any technique for vaginal hysterectomy, the importance of the cardinal and uterosacral ligaments to support the vaginal vault must be constantly borne in mind. He criticizes the Mayo technique because

it fails to utilize these supports and, therefore, the incidence of cul-de-sac hernia following the operation is high. Surgical procedure evolved by him is as follows:

Cervix grasped with tenaculum; transverse incision over anterior cervix; anterior vaginal mucosa dissected from bladder with scissors; vesicovaginal fascia separated from the mucosa; incision carried around posterior vaginal cuff and the cul-de-sac opened with scissors; uterosacral ligaments grasped with Heaney clamps, cut and tied; the anterior cul-de-sac is opened; the lateral cervical tissue, including the lower border of the cardinal ligaments, is cut and ligated, leaving the ligatures on both the uterosacral and cardinal ligaments long; the broad ligaments are then ligated and allowed to retract; on reaching the top of the broad ligament the ovarian ligaments and the tubes are ligated; the uterosacral ligaments and the cardinal ligaments are sutured to the posterior vaginal cuff, thus supporting the vagina and closing the cul-de-sac.

Cystocele and methrachele are treated by suturing over the previously dissected fascia. The mucosa is closed with interrupted chromic.

The posterior vaginal relaxation is then corrected by high approximation of recto-vaginal fascia and closure of vaginal mucosa.

WILLIAM BICKERS.

Miscellaneous

Martin, Gustav: Chronic Avitaminosis E in the Castrate and Non-Castrate Rat, *Am. J. of Physiol.* 148: 344-349, 1947.

Martin, using six series of fifty rats in each group, including two series of controls, found that chronic avitaminosis E symptomatically ran a markedly different course in the castrate and noncastrate rat. Three lines of evidence exhibited the effect of castration on this vitamin deficiency state. In the deficient E and castrate series the life spans were prolonged; the weight curves improved and there was a marked accumulation of fat.

The histopathology of the testis in avitaminosis E, in rats, is well known. There is irreversible degeneration of germinal epithelium. The Sertoli cells remain. It is the generally accepted view, according to Martin, that the interstitial cells of the testis are sources of androgen. Testosterone brings about spermatogenesis by stimulating the pituitary to secrete gonadotrophic hormones. Martin notes in his discussion, however, there seems to be no report of the testosterone content of testicles in the avitaminotic E rat.

C. E. FOLSOME.

Bessis, M.: A New Biologic Test to Detect Anti-Rh Immunization, *Gynec. et Obst.* 45: 493, 1946.

If two intravenous injections of Rh-positive blood, 0.5 c.c. each, are given to an Rh-negative individual, titration of his blood for anti-Rh agglutinins one week later will clearly indicate a prior isoimmunization. Thirty Rh-negative volunteers failed to develop any agglutinins, whereas four women who had previously borne erythroblastotic infants developed titers in the range of 1:128 (which disappeared in sixty days). The author suggests this procedure to determine Rh factor responsibility where there is a history of atypical transfusion reaction, or of repeated fetal misadventures of various kinds. It is argued that the dose of Rh-positive blood is too small to cause a reaction in persons already strongly sensitized, or to cause an original sensitization.

IRVING L. FRANK.

Newborn

Tortora, M.: Vaginal Smears in the Genital Crisis of Female Infants, *Arch. di Ostet. e Ginec.* 51: 290, 1946.

The author reviews the literature on the subject of cyclic variations in the vaginal mucosa of sexually mature women and compares cell types present during the monthly cycle to cell types present in vaginal smears taken during the genital crisis of female infants.

In a series of thirty infants—twenty-one born at term and nine premature—vaginal smears were taken daily for a period of ten days. Besides cell types, the vaginal flora and pH were determined.

In the first three days, deep cells of Shorr's type II and intermediate pienotic cells are predominant, but some cells of Shorr's type IV with fine granulations of the cytoplasm, and some completely cornified cells are present.

On the fourth to fifth days, deep cells of type I, small oval cells with sharp outlines appear, and deep cells of type II increase, while the intermediate and cornified cells diminish.

From six to ten days, intermediate cells disappear, while cells of type II seem to predominate again. Leucocytes, red blood corpuscles, and mucus are abundant in this period. The pH shows at birth a value of 5.5, and becomes lower during the next days. On the first day, the vaginal secretion is usually sterile. On the second day, cocci are predominant, and starting with the third day, Döderlein bacilli appear. In premature infants, the differences in the cellular types are less evident.

GEMMA BAEZILAL.

Pregnancy

Vara, Paavo: On Late Second Childbirths, *Ann. Chirurg. et Gynec. Fenniae* 35: 20-40, 1946.

The author reviews the obstetric data on 1,606 late secundipara cases, in which the time interval between deliveries had been at least six years, at the University of Helsinki's Women's Clinics I and II, in the interval of 1927 to 1944. As control data he selects a series of 3,680 secundipara cases wherein the second delivery occurred less than the longer six-year period in his study series. Among the 1,606 late secundipara cases, 92.77 per cent were spontaneous deliveries, 5.11 per cent were operative, 2.18 per cent breech presentations, and 0.25 were deflexion presentations. As the interval between deliveries was extended, the author observed that 75 per cent of his case material were over 30 years of age, while the 40-year-old patients were present in larger number in special group of late secundiparas as compared to secundiparas in the control series.

The duration of labor—thirteen hours and twenty-one minutes—was greater in the late secundiparas than in the control group. This increase in duration resulted from a lengthening of the first stage (twelve hours and forty minutes), while the duration of the second stage (twenty-seven minutes) and third stage (fourteen minutes) did not differ from the control series.

Premature rupture of the membranes showed an increased incidence among the late secundipara but seemed to show no negative effect upon prognosis. The incidence of operative deliveries among the late secundipara than among the secundipara bearing children less than six years apart. The prognosis of mother and infant was no poorer in the study group when compared to the control group. The study group, 1,606 cases, gave a maternal mortality of 0.06 per cent, and infant mortality of 1.00 per cent.

The incidence of postpartum hemorrhage showed a marked increase, but only in those cases delivering premature infants.

The author concludes that we are justified in holding as unfounded the fear among parturients that childbirth offers special difficulties in cases where a long interval has elapsed between deliveries. The only exception was in that smaller group of late secundiparas where an interval of fifteen years supervened. These cases in particular should be hospitalized.

C. E. FOLSONE.

Ingerslev, Magens, and Teilum, Gunnar: Biopsy Studies on the Liver in Pregnancy. I. Normal Histological Features of the Liver as Seen on Aspiration Biopsy, *Acta obst. et gynec. Scandinav.* 25: 339-351, 1945.

The authors, reporting from the Lying-In Department of the Rigshospital, Copenhagen, reviewed the literature upon the subject of the histologic picture of the liver in normal pregnancy. The writers contend that aspiration biopsy of the liver through the midaxillary line, under ether or chloroform anesthesia, at the time of other surgical procedures. In the six

nonpregnant women free of symptoms of liver lesions, the major surgical procedures, beyond liver aspiration biopsy, included dilatation of the cervix in two instances and along with a cervical amputation, a ventrosuspension of the uterus, a salpingo-oöphorectomy and a bilateral salpingectomy in the four remaining cases. The liver specimen was fixed in ten per cent formalin, else Helly's fluid and stained with hematoxylin-eosin or by the van Gieson-Hansen method. Some of the specimens were stained also with Sudan III or Best's carmine stain.

The authors are of the opinion that this data, supplemented by experimental findings (rats and rabbits), demonstrates that the light and dark liver cells—Forsgren phases in human liver—are produced by the fixative used and probably due to a more rapid fixation of the cells in the marginal zone—in contrast to the central part of the specimen where the water phase of the fixative fluid asserted itself more strongly to bring about an absorption of water by the cells, which swell before their fixation becomes pronounced. No histological evidence was found which might indicate rhythmic phases in human liver function. The writers consider this evidence representative and reliable data as the basis for studies on the structure of liver tissue in biopsy specimens under morbid conditions. Their paper is accompanied by one chart and four photomicrographs.

C. E. FOLSOME.

Labor

Odell, L. D., Randall, J. H., and Scott, G. W.: Prolonged Labor With Special Reference to Postpartum Hemorrhage, *J. A. M. A.* 133: 735, 1947.

The authors define a prolonged labor as one lasting thirty hours, one that terminates within three hours as precipitate, and the remainder as normal. When the total blood loss is 600 c.c. or more a diagnosis of postpartum hemorrhage is made. Prolonged labors formed 2.7 per cent of the total number of deliveries over a six-year period with primiparas forming 66.9 per cent of this group. The principal causes of prolonged labor are cephalopelvic disproportion, abnormal fetal presentations, and uterine inertia. In the authors series uterine inertia was the principal cause of prolonged labor. Postpartum hemorrhage was more frequent following prolonged labor. In some cases the bleeding was due to prolonged anesthesia and the trauma of operative deliveries, but in nonoperative deliveries the bleeding was due to postpartum uterine atony. The authors recommend in these cases careful conduct of the third stage, early uterine massage, and the use of oxytocic drugs, as well as, the use of fluids and whole blood when necessary.

WILLIAM BERMAN.

Schlicke, Carl P.: Ectopic Endometrial Tissue in the Thigh, *J. A. M. A.* 132: 445, 1946.

The author reports a case of a 35-year-old Filipino woman with a tumor on the posterior aspect of the left thigh. Three years prior to admission she began to suffer from pain and tenderness in a circumscribed area on the posterior aspect of the left thigh during her menses. The mass grew larger and more painful. The tumor mass was removed and on microscopic examination showed the typical structure of an endometrioma.

WILLIAM BERMAN.

Venereal Disease

Perkins, George E., and Brewster, Harold N.: Penicillin in the Treatment of Gonorrhea in Women, Results of Treatment as Reported by Twelve Cooperating Venereal-Disease

Clinics in Massachusetts During 1945, *New England J. Med.* 236: 277, 1947.

This study was based on the tabulation of information sent in by twelve cooperating clinics in Massachusetts regarding cases of gonorrhea in women who had been treated with varying courses of intramuscular injections of an aqueous solution of penicillin. Two hundred and thirty-four courses of treatment were given in two hundred cases. The best results were obtained by the use of 150,000 units or more of penicillin divided into three equal doses spaced at two hour intervals.

The authors state that the application of penicillin seems to be the outstanding advance to date in the therapy of gonorrhea. The results so striking that all other forms of therapy now seems antiquated.

JAMES P. MARR.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Emil Novak, Baltimore, Md. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be held at Williamsburg, Va., May 24, 25, and 26, 1948.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Aaron E. Kanter. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, W. O. Johnson. *Secretary*, W. E. Oldham, 842 Barrett Avenue, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Joseph A. Hepp. *Secretary*, Clarence H. Ingram, Jr., 6004 Penn Avenue, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, Paul Gustafson. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society.** (1933) *President*, William J. Cusack. *Secretary*, John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Dr. Earl Conway Smith. *Secretary*, John S. Herring, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society.** (1924) *President*, Joseph A. Hardy, Jr. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Warren E. Massey. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, John Boyd. *Secretary-Treasurer*, William Durwood Suggs, Monument Ave. and Lombardy St., Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, H. J. Lesnick. *Secretary*, Mark Daniel, 2344 Davidson Ave., Bronx 53, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, S. B. Conger. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Everett C. Hartley. *Secretary*, John Haugen, 100 E. Franklin Ave., Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Charles F. Moon. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Samuel A. Cosgrove. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Colin C. McCorriston. *Secretary-Treasurer*, K. S. Tom, 296-E South Vineyard Street, Honolulu 39, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Duncan R. Neilson. *Secretary-Treasurer*, David M. Baker, 520 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1947) *President*, William Benbow Thompson. *Secretary*, Woodward D. Beacham, 1430 Tulane Ave., New Orleans 13, La.

Items

Notice to Diplomates

American Board of Obstetrics and Gynecology, Inc.

The forthcoming fourth edition of the Directory of Medical Specialists plans to designate by appropriate abbreviations whether Diplomates of the above Board practice both branches of the specialty or major in one or the other. The letters OG will be used to indicate combination of practice in both branches, the letter O that the Diplomate majors in obstetrics, and the letter G that he majors in gynecology.

Diplomates who have not already notified the Directory Publication office on this matter in making their biographic returns should communicate with the Directory of Medical Specialists, 210 East Ohio Street, Chicago, Illinois.

PAUL TITUS, M.D.
Secretary.

Committee on Human Reproduction of the National Research Council

The Committee on Human Reproduction of the National Research Council, acting for the National Committee on Maternal Health, Inc., announces that it will entertain applications for grants for research in the field of reproduction. Applications to become effective 1 July 1948 will be received until 1 May 1948; applications to become effective 1 October 1948 will be received until 1 August 1948.

The Committee will consider support of biological, clinical, economic, medical, psychological and sociological research dealing broadly with the field of human reproduction in general and with respect to specific problems including maternal and fetal physiology, the factors controlling conception, the physiology of fertilization and conception, and sterility. For the year 1948-49, the Committee will place specific emphasis upon investigations of the factors controlling conception, fertility, and sterility, but other fields of endeavor will be supported if projects of special significance are presented. In subsequent years, changing emphasis may be anticipated.

The National Committee on Maternal Health has advised the National Research Council that it proposes to solicit funds to finance the program of research recommended by the Committee on Human Reproduction to an amount of approximately \$200,000 for 1948-49.

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NOW AND THEN*

A Statistical Review of the Progress of Midwifery During the Last Twenty Years With Thoughts for the Future

W. F. T. HAULTAIN, O.B.E., M.C., M.B., B.CH., F.R.C.P.E.,
F.R.C.S.E., F.R.C.O.G., EDINBURGH, SCOTLAND

JOSEPH PRICE made himself famous for all time by his splendid work on inflammatory conditions in the pelvis and by being the first to coordinate gynecology and abdominal surgery. His outstanding career was prefaced when, at only 24 years of age, he was appointed to the charge of the Obstetrical Department of the Philadelphia Dispensary; ten years later, to demonstrate that his interest in obstetrics was still very much alive, he took charge of the Preston Retreat and, during his seven years of duty there, no death was recorded from sepsis, a most noteworthy and unique achievement for those days. His was the enviable record of being the first to try and put obstetrics on an aseptic basis.

I may therefore be excused tonight for choosing a purely obstetric subject for this oration, which honors his memory. My title is "Now and Then" and records the progress of midwifery during the last twenty years.

There have been great advances in medicine and surgery during the last twenty years, but has midwifery also progressed? I propose to answer this question in the affirmative, and it is my endeavor to state what I take to be the main reasons for such success and even to suggest how further improvement might be achieved. In order to substantiate this claim, I have delved into the hospital reports for the past twenty years of five of the largest maternity hospitals in the British Isles and of the New York Lying-In Hospital. It is the result of these investigations that I intend to present. The first hospital which I have selected is the old Edinburgh Royal Maternity and Simpson Memorial Hospital and the new Simpson Maternity Pavilion of the Royal Infirmary, Edinburgh, to which the patients were transferred in March, 1939, because I have been a member of the Honorary Staff during these twenty years. (These hospitals are referred to as "The Simpson" in the Tables and Charts.) They com-

*The Joseph Price Oration for 1947, delivered at the Forty-eighth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1947.

memorate the name of Sir J. Y. Simpson, the centenary of whose discovery of the anesthetic and analgesic properties of chloroform is to be celebrated in November of this year. Simpson himself worked at the old Edinburgh Lying-in Hospital, which preceded the Simpson, so many of his case records are still in existence in the Hospital files. The other British hospitals are the Glasgow Royal Maternity Hospital and St. Mary's Hospital, Manchester, together with the Rotunda and the Coombe Hospitals in Dublin.

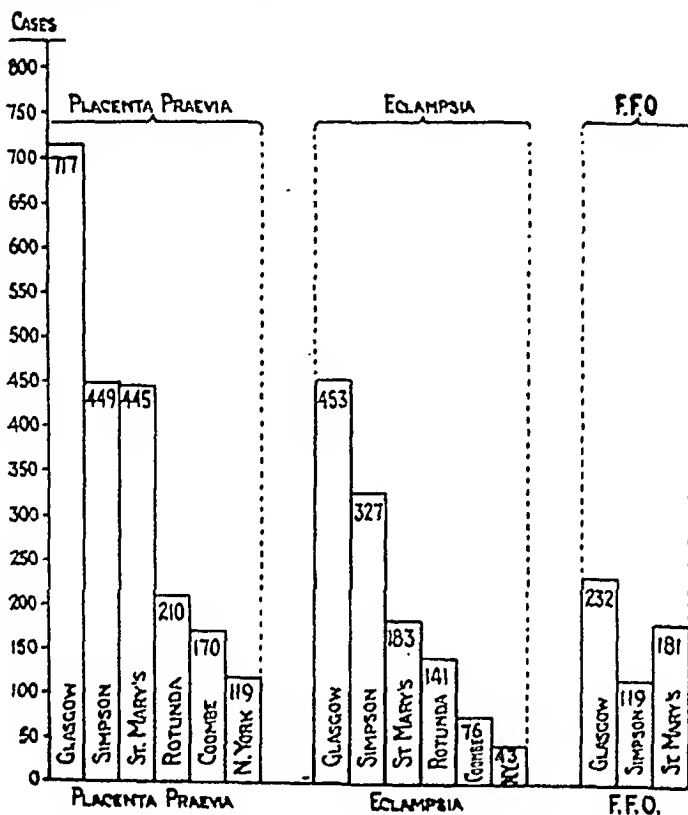


Fig. 1.—Comparison of hospitals with regard to some abnormalities during the last ten years.

In Great Britain and Ireland the large maternity hospitals all admit a varying number of antenatal and intrapartum emergency cases from general practitioners. These cases are termed "non-booked" cases, and are often admitted in anything but good condition, especially if admitted when in labor. These hospitals serve large areas and their emergency admissions vary as to numbers and severity; for instance, in the Glasgow Hospital, 55 to 60 per cent are emergency cases; at St. Mary's, 55 per cent; at the Simpson, 25 per cent; and at the Rotunda and the Coombe, 20 per cent. An indication of the numbers and the types of these conditions during the past ten years is shown in Fig. 1.

Placenta previa—

Glasgow, 717; Simpson, 449; St. Mary's, 445; Rotunda, 210; Coombe, 170; New York, 119.

Eclampsia—

Glasgow, 453; Simpson, 327; St. Mary's 183; Rotunda, 141; Coombe, 76; New York, 43.

Failed forceps outside—

Glasgow, 232; St. Mary's, 181; Simpson, 119; Rotunda, Coombe, and New York, not mentioned.

The Glasgow area embraces a population of well over two million and is in parts very poor and even squalid; rickets is still rife, though diminishing, and many of the emergency cases do not yet avail themselves of the antenatal supervision provided. St. Mary's Hospital, Manchester, also serves a large industrial population, but there are other smaller hospitals in the district which help to relieve it, and the population appears to have a better appreciation of the value of antenatal care. Though the Simpson Hospital, Edinburgh, admits practically all the emergency cases from the South East of Scotland, there is not the same poverty in this area, and practically all the emergency cases have had at least some antenatal supervision, maybe at times inadequate, by their general practitioners. The Dublin hospitals under review are two of three large maternity

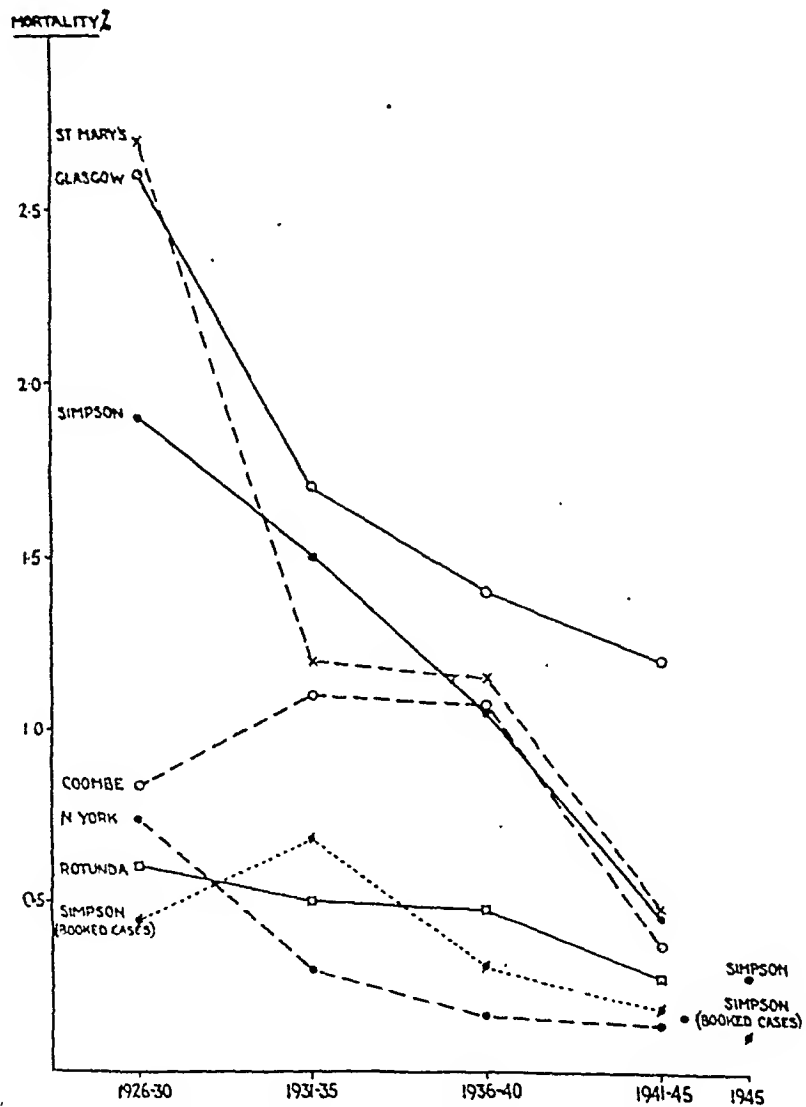


Fig. 2.—Mortality rates for six hospitals for four five-year periods.

institutions which serve the Dublin area, and therefore the emergency cases are divided. It is the admission of these "non-booked" cases which raises the maternal mortality and morbidity rates to compare unfavorably with hospitals which admit only cases supervised antenatally by their own staff. This important fact is also exemplified by contrasting the greatly decreased mortality and

morbidity in the "booked" cases (i.e. those who have attended the hospital antenatal clinics before admission) with the total mortality and morbidity of the hospital or with that of the "non-booked" cases. Again, a large number of the "booked" cases at all the hospitals are abnormal, being referred early to the hospital antenatal clinic, because of suspected dystocia or a bad obstetric or medical history; in Glasgow over 70 per cent of the total admissions are abnormal. The great decrease in the "booked" mortality figures as compared with the "non-booked" is very clearly seen in the mortality graphs of the last twenty years from the Simpson. (You will notice also that for the year 1945 alone the mortality rate is 0.28 per cent for all cases but is only 0.12 per cent for the "booked" cases, a point I wish to refer to again later.)

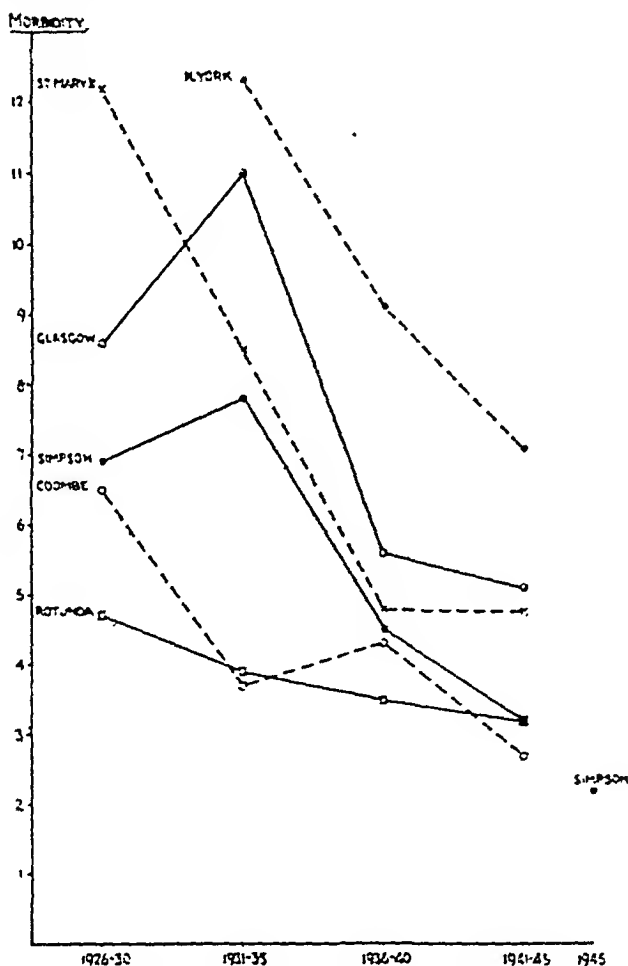


Fig. 3.—Morbidity rates for six hospitals.

The efficiency and obstetric reputation of a maternity hospital are primarily judged by its maternal mortality and morbidity and by its stillbirth and neonatal death rates. If, therefore, these rates show a marked decrease in the past twenty years, then one can justifiably assume that midwifery has progressed. The graphs of these rates for the various hospitals for five-yearly periods, beginning in 1926 and ending in 1945, to which I would now draw your attention, would appear to give striking evidence as to the progress midwifery has made during these years; all these rates are definitely lowered in all the

hospitals and though the mortality statistics of the New York Lying-In Hospital would seem to put the British hospitals to shame, it would not appear to be so bad as it seems at first sight, in so far as, in the case of the New York hospital, most of these cases seem to come under the "booked" category, and the figures for the Simpson "booked" cases for 1945 approach those of New York quite closely.

Morbidity for the British and Irish hospitals has been gauged by the B.M.A. standard as "All fatal cases and all cases in which the temperature reaches 100 degrees F. in any two of the bi-daily readings from the end of the first day to the end of the eighth day after delivery"; the morbidity standard for the Lying-In Hospital, New York, however, is more strict, as the temperature is taken four-hourly, which probably accounts for its higher rate. These graphs show how morbidity has decreased.

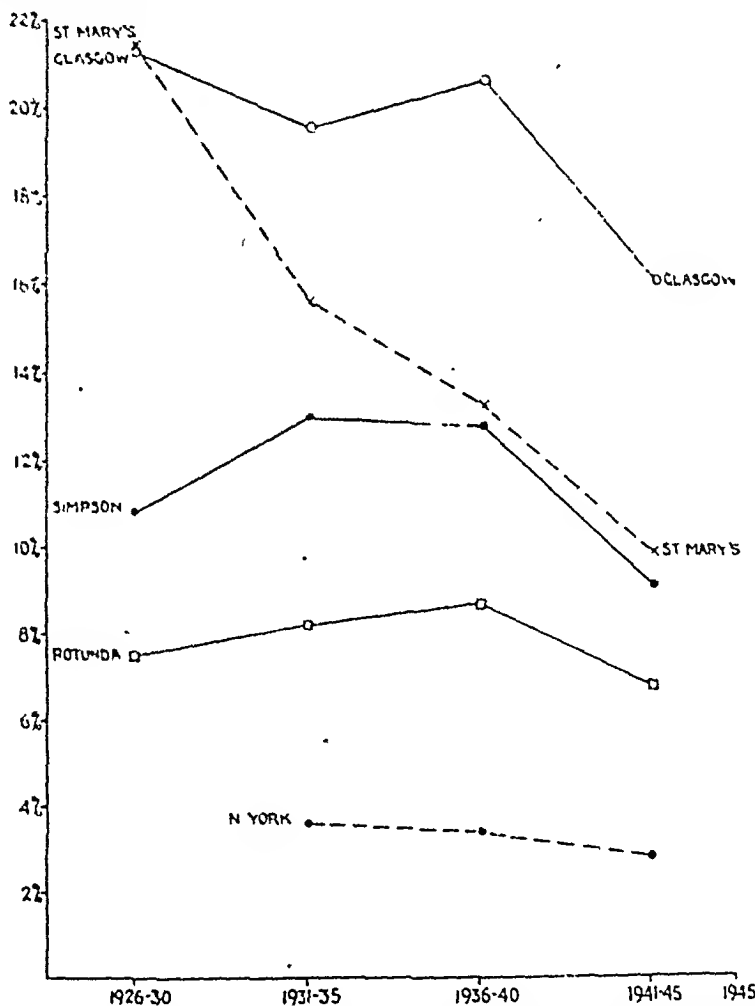


Fig. 4.—Stillbirths and neonatal deaths. Percentage of all cases at five hospitals.

Accepting that obstetric results have improved generally, I now propose to indicate in what direction this improvement has been achieved. I have tabulated the main causes of death in these hospitals for five-yearly periods, 1926 to 1930, 1931 to 1935, 1936 to 1940, and 1941 to 1945. These show, in the first place, how the hospitals compare with one another with regard to the causes of deaths, second, how the totals of deaths from the various causes have decreased

TABLE I. PRINCIPAL CAUSES OF DEATH (IN ORDER OF FREQUENCY)
The Simpson, Edinburgh

CAUSE	1926-30 TOTAL ADMISSIONS—10,749			1931-35 11,652			1936-40 13,372			1941-45 18,640		
	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE
Eclampsia	50	0.46	Sepsis	38	0.33	Sepsis	26	0.19	Eclampsia	15	0.08	
Sepsis	28	0.26	Cardiac	19	0.16	Eclampsia	15	0.11	Sepsis	14	0.07	
Pre-eclampsia	14	0.13	Eclampsia	15	0.13	Pre-eclampsia	13	0.09	Cardiac	9	0.05	
Rupture	14	0.13	Pre-eclampsia	15	0.13	P.P.H. and Shock	13	0.09	P.P.H. and Shock	8	0.05	
Pl. Praevia	12	0.11	P.P.H. and Shock	11	0.09	Cardiac	11	0.08	Rupture	4	0.02	
Hyperemesis	12	0.11	Pl. Praevia	11	0.09	Hyperemesis	9	0.07	Pl. Praevia	2	0.01	
Cardiac	11	0.10	Hyperemesis	8	0.07	Pl. Praevia	8	0.06	Pre-eclampsia	2	0.01	
P.P.H. and Shock	8	0.07	Rupture	8	0.07	Rupture	6	0.04	Acc. Haem.	1	0.005	
Acc. Haem.	7	0.06	Acc. Haem.	3	0.03	Ret. Placenta B.O.	6	0.04	Hyperemesis	0		
Ret. Placenta B.O.	2	0.02	Ret. Placenta B.O.	1	0.009	Acc. Haem.	4	0.04	Ret. Placenta B.O.	0		

TABLE II. PRINCIPAL CAUSES OF DEATH (IN ORDER OF FREQUENCY)
Glasgow R.M.H.

CAUSE	1926-30 TOTAL ADMISSIONS—19,806			1931-35 22,433			1936-40 23,113			1941-45 21,944		
	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE
Eclampsia	64	0.32	Eclampsia	51	0.23	P.P.H. and Shock	44	0.19	P.P.H. and Shock	37	0.17	
Sepsis	59	0.30	Sepsis	35	0.10	Eclampsia	35	0.15	Sepsis	35	0.16	
Pl. Praevia	52	0.26	Pl. Praevia	31	0.14	Sepsis	34	0.15	Eclampsia	34	0.15	
Pre-eclampsia	43	0.20	Cardiac	31	0.14	Cardiac	29	0.13	Cardiac	24	0.11	
Hyperemesis	38	0.15	Acc. Haem.	31	0.14	Acc. Haem.	20	0.09	Ret. Placenta B.O.	24	0.11	
Cardiac	34	0.17	P.P.H. and Shock	18	0.08	Hyperemesis	19	0.08	Rupture	17	0.075	
Acc. Haem. P.P.H. and Shock	26	0.13	Hyperemesis	18	0.08	Rupture	18	0.08	Acc. Haem. Pl. Praevia	14	0.06	
Rupture	20	0.1	Pre-eclampsia	16	0.07	Ret. Placenta B.O.	17	0.07	Pre-eclampsia	12	0.05	
Ret. Placenta B.O.	17	0.09	Ret. Placenta B.O.	15	0.06	Pre-eclampsia	14	0.06	Hyperemesis	7	0.03	
	16	0.08	Rupture	14	0.05	Pl. Praevia	12	0.05		7	0.03	

in the successive quinquennial periods, and, third, how each cause of death is related in percentage to the total admissions.

The majority of maternal deaths comes under three main headings: (1) sepsis, (2) toxemia, and (3) hemorrhage, and Table VII shows a comparison of the percentage of deaths under these three headings occurring during the last ten years in these hospitals and also figures for some other American hospitals, as well as the total percentages for the U.S.A. for 1941.

Let us now examine the main causes of maternal mortality individually and in more detail, to see if improvement has been achieved for each cause, and to attempt to give explanations for such improvement. As sepsis would seem to be the most common cause of death from the U.S.A. figures for the past ten years, and is a common cause in the British Isles as well, I propose to consider this subject first.

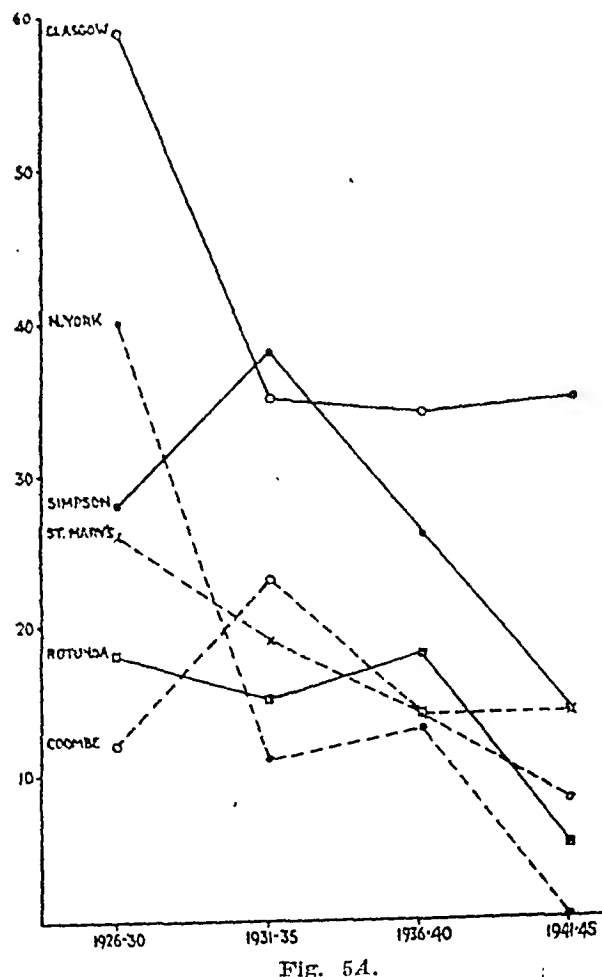
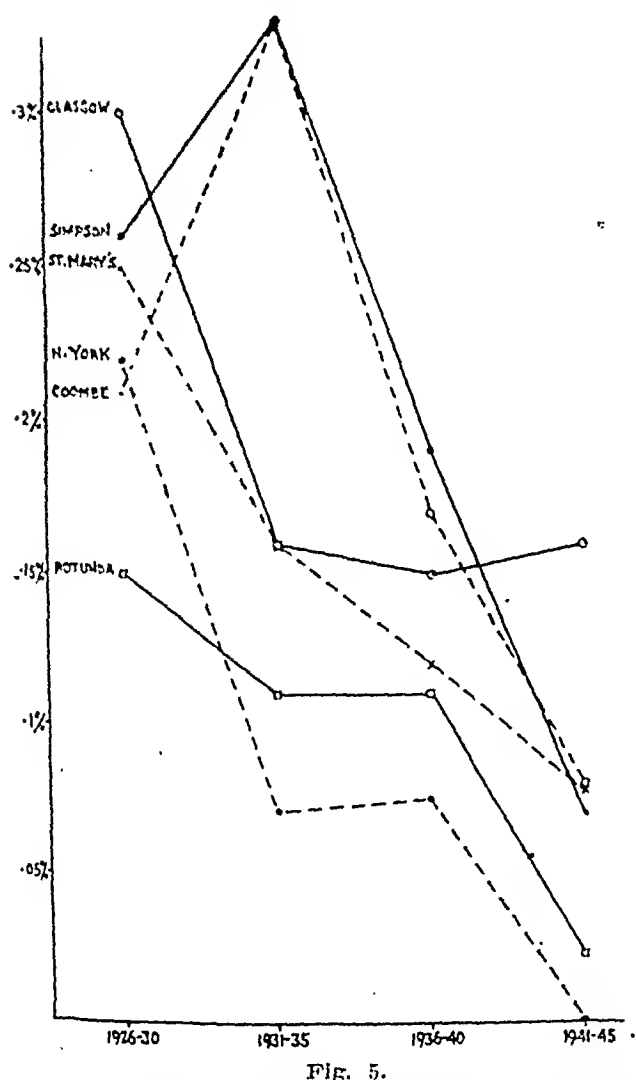


Fig. 5.—Sepsis. Mortality percentage of total admissions for six hospitals.

Fig. 5A.—Sepsis. Number of deaths in six hospitals.

Sepsis

The incidence of puerperal sepsis, as seen from the morbidity graph and Table VIII, has decreased in all the hospitals with the exception of the Rotunda, and the deaths from sepsis have also decreased, with the exception of Glasgow,

TABLE III. PRINCIPAL CAUSES OF DEATHS (IN ORDER OF FREQUENCY)
St. Mary's Hospital, Manchester

1926-30			1931-35			1936-40			1941-45		
TOTAL ADMISSIONS—10,178			11,876			11,904			18,091		
CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS
Sepsis	26	0.25	P.P.H. and Shock	25	0.21	P.P.H. and Shock	24	0.20	Sepsis	14	0.077
P.P.H. and Shock	26	0.25	Sepsis	19	0.16	Eclampsia	18	0.15	Cardiac	12	0.066
Cardiac	17	0.16	Eclampsia	18	0.15	Pre-eclampsia	17	0.14	Eclampsia	10	0.055
Eclampsia	17	0.16	Cardiac	13	0.11	Cardiac	16	0.13	P. P. H. and Shock	10	0.055
Pl. Praevia	13	0.13	Acc. Haem.	13	0.11	Sepsis	14	0.12	Pl. Praevia	7	0.038
Acc. Haem.	12	0.12	Pre-eclampsia	12	0.10	Hyperemesis	12	0.10	Pre-eclampsia	2	0.011
Hyperemesis	11	0.11	Pl. Praevia	9	0.08	Acc. Haem.	11	0.09	Ret. Placenta	2	0.011
Ret. Placenta	10	0.10	Hyperemesis	7	0.06	Pl. Praevia	6	0.05	Hyperemesis	1	0.006
B.B.O.	9	0.09	Ret. Placenta	6	0.05	Ret. Placenta	6	0.05	Acc. Haem.	1	0.006
Pre-eclampsia	9	0.09	B.B.O.	2	0.02	Rupture	3	0.025			
Rupture	7	0.07	Rupture	2	0.02						

TABLE IV. PRINCIPAL CAUSES OF DEATHS (IN ORDER OF FREQUENCY)
Rotunda

1926-30			1931-35			1936-40			1941-45		
TOTAL ADMISSIONS—11,914			14,245			16,900			21,351		
CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS
Sepsis	18	0.15	Sepsis	15	0.11	Sepsis	18	0.11	Eclampsia	10	0.047
Eclampsia	13	0.10	Eclampsia	8	0.056	Acc. Haem.	11	0.065	Rupture	6	0.028
P.P.H. and Shock	7	0.06	P.P.H. and Shock	8	0.056	Eclampsia	9	0.053	Sepsis	5	0.023
Cardiac	6	0.05	Cardiac	6	0.04	P.P.H. and Shock	8	0.046	Pre-eclampsia	5	0.023
Pre-eclampsia	5	0.04	Pre-eclampsia	6	0.04	Pl. Praevia	5	0.03	Cardiac	4	0.019
Acc. Haem.	4	0.03	Acc. Haem.	4	0.028	Pre-eclampsia	3	0.018	P.P.H. and Shock	4	0.019
Rupture	4	0.03	Pl. Praevia	4	0.028	Rupture	3	0.018	Acc. Haem.	3	0.014
Hyperemesis	3	0.025	Rupture	2	0.01	Hyperemesis	2	0.012	Pl. Praevia	3	0.014
Pl. Praevia	1	0.008	Hyperemesis	2	0.01	Ret. Placenta	1	0.006	Hyperemesis	1	0.003
					B.B.O.						

where they have remained pretty stationary for the past fifteen years. It is interesting to note that, though the morbidity rate in the N. Y. Lying-In Hospital is higher than that of our hospitals, there has been no death from sepsis there during the past five years, an achievement which deserves the highest praise. It might be of passing interest to record that, at the Simpson during the year 1936, every patient after delivery received a dose of calcium sulfide, 2 grains, 3 times a day, for four days and during that year the morbidity, which had previously never been lower than 6 per cent (usually between 7 and 8 per cent) dropped to 4.3 per cent. During the following year every patient had prophylactic sulfonamide for three days after delivery and the morbidity dropped further to 3.4 per cent, which was the lowest figure recorded, even though we moved into the new hospital in 1939, until the years 1944 and 1945, when the morbidity has been 2.9 per cent and 2.2 per cent respectively. There is no doubt that the introduction of the sulfonamides has proved of great benefit in reducing the morbidity in all these hospitals. At the Simpson we do not give sulfonamide as a routine now, but if any patient has been liable to infection, then she receives a prophylactic course. This prophylactic practice is believed to have reduced the incidence of sepsis, but if sepsis actually develops, then it would seem that the sulfonamides have not lowered the percentage mortality very appreciably. This is also shown with regard to the other hospitals, with the exception of the Rotunda. (Table VIII.) It is too early yet to know how the discovery of penicillin will affect the incidence and the mortality rate of sepsis, but we are hopeful that its use will lower both rates still further.

Besides the introduction of the sulfonamides, to what other causes may this improvement in morbidity and mortality from sepsis be attributed? The greatest reductions occur in the British, as distinct from the Irish, hospitals, at a time when Britain was in the throes of war, when food was scarce, and many of the cities had suffered greatly from bombing. The people would, therefore, be expected to be undernourished, overanxious, and an easy prey to infection; during the whole period the hospital staffs were severely depleted and overworked and the hospitals grossly overcrowded; a completely aseptic technique was impossible to achieve, owing to the shortage of materials, and, at the Simpson, gloves have not been worn, except for cesarean sections, since 1942, as they were unobtainable in sufficient quantity. It is remarkable, therefore, that, for the years 1944 and 1945, when circumstances were absolutely at their worst, there were only two deaths from sepsis at the Simpson. It is indeed difficult to reconcile these facts, but I think the improvement may have been due to several causes: (1) *Dietetic*: Though the majority of people were underfed during these five years, the mother-to-be was privileged, and she received a pint of milk extra a day, as well as Vitamins A, D, and C, if need be, free of charge. These, of course, were readily obtainable pre-war, but it was only when the pregnant woman realized she was getting something no one else could obtain, and that free if need be, that she really took full advantage of this dietary, which she had never done previously. This helped, to a large extent, to increase the natural resistance to infection. (2) All pregnant women had to visit their doctors or antenatal clinics to get the necessary certificate for the

TABLE V. PRINCIPAL CAUSES OF DEATHS (IN ORDER OF FREQUENCY)
Coombe Hospital, Dublin

1926-30 TOTAL ADMISSIONS—5619				1931-35 7010				1936-40 8189				1941-45 9965			
CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	
Sepsis	12	0.21	Sepsis	23	0.33	Sepsis	14	0.17	Sepsis	8	0.08	Sepsis	8	0.08	
Pl. Praevia	8	0.14	Pl. Praevia	5	0.07	Cardiac	9	0.11	P.P.H. and Shock	5	0.05	P.P.H. and Shock	5	0.05	
Cardiac	4	0.07	Acc. Haem.	5	0.07	Acc. Haem.	7	0.09	Acc. Haem.	3	0.03	Acc. Haem.	3	0.03	
Acc. Haem.	4	0.07	Cardiac	4	0.06	P.P.H. and Shock	7	0.09	Pl. Praevia	2	0.02	Pl. Praevia	2	0.02	
P.P.H. and Shock	4	0.07	Eclampsia	4	0.06	Pl. Praevia	6	0.07	Eclampsia	2	0.02	Eclampsia	2	0.02	
Hyperemesis	4	0.07	P.P.H. and Shock	4	0.06	Eclampsia	5	0.06	Rupture	1	0.01	Rupture	1	0.01	
Eclampsia	3	0.05	Hyperemesis	3	0.04	Hyperemesis	4	0.05	Hyperemesis	4	0.05	Hyperemesis	4	0.05	
Rupture	2	0.04	Rupture	2	0.03	Pre-eclampsia	4	0.05	Pre-eclampsia	4	0.05	Pre-eclampsia	4	0.05	
						Rupture	1	0.01	Rupture	1	0.01	Rupture	1	0.01	

TABLE VI. PRINCIPAL CAUSES OF DEATHS (IN ORDER OF FREQUENCY)
New York Lying-In Hospital

1926-30 Total Admissions—17,790				1931-35 14,166				1936-40 17,501				1941-45 19,763			
CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	CAUSE	NUM- BER	PERCENT- AGE OF ADMIS- SIONS	
Sepsis	40	0.22	Sepsis	11	0.07	Sepsis	13	0.07	Embolus	6	0.03		6	0.03	
P.P.H. and Shock	18	0.10	P.P.H. and Shock	5	0.04	Cardiac	6	0.03	Cardiac	4	0.02		4	0.02	
Cardiac	13	0.07	Embolus	4	0.03	P.P.H. and Shock	4	0.024	P.P.H. and Shock	2	0.01		2	0.01	
Pre-eclampsia	12	0.07	Acc. Haem.	3	0.02	Cerebro-vasc.	3	0.017					2	0.01	
Rupture	10	0.06	Cardiac	2	0.01	Embolus	3	0.017	Cerebro-vasc.	2			2		
Eclampsia	7	0.04	Rupture	2	0.01	Acc. Haem.	2	0.012							
Embolus	4	0.02	Pre-eclampsia	2	0.01	Hyperemesis	2	0.012							
Acc. Haem.	2	0.01	Eclampsia	1	0.007	Pl. Praevia	1	0.006							
						Rupture	1	0.006							
						Eclampsia	1	0.006							

TABLE VII. PERCENTAGE OF THE TOTAL DEATHS, 1936-45 .

	SEPSIS	TOXAEMIA	HAEMORRHAGE
Simpson	18.2 (25.2)	24.5 (30.7)	19.9 (14.8)
Glasgow R.M.H.	11.7 (10.3)	19.7 (25.2)	30.6 (21.8)
St. Mary's	13.3 (12.2)	22.1 (20.1)	29.2 (27.9)
Rotunda	18.0 (23.3)	23.4 (25.8)	27.3 (19.6)
Chicago Lying-in	39.5	7.4	16.0
Cook County Hospital	23.5	17.6	12.6
N. Y. Lying-In	19.4 (30.9)	4.5 (13.3)	13.4 (16.9)
U. S. A. (1941)	38	25	25
Brooklyn (8 years)	150 cases	110 cases	208 cases

Figures in parentheses indicate previous 10-year (1926-35) percentage.

extra milk and vitamins and also for extra coupons for clothing, mostly for the baby, the milk certificate having to be renewed at frequent intervals; thus every pregnant woman received antenatal care, which many would not have troubled to obtain if there had been no certificates to be signed. This was probably an important factor in decreasing the mortality and morbidity rates in general, but especially with the unbooked cases. (3) As the general practitioners were so overworked, they had neither the time nor the inclination, in many instances, to undertake midwifery, so that, in the main, antenatal care was carried out at clinics, and the patients thus came under skilled observation throughout pregnancy. (4) As nurses were scarce and home helps impossible to obtain, nearly every primipara was delivered in hospital or in a nursing-home; thus the number of infected non-booked cases admitted were reduced. (5) In this connection, also, the effect of the intensive midwifery instruction of the students, which had been carried out for about fifteen years previously, was beginning to bear fruit, and the practitioner realizing his limitations sent the difficult case into hospital, thus avoiding dangerous interference in the patient's own home. This is exemplified from the records, which show that the caesarean section mortality at the Simpson dropped from the previous figure of 3.4 per cent to 1.9 per cent for the last five years. (6) The extended use of the lower uterine segment caesarean section, (7) the more frequent use of blood transfusion, and (8) the better administration of anaesthesia; resident well-qualified anaesthetists, always available for difficult cases, have undoubtedly played their part. (9) The introduction of Dettol, a most efficient antiseptic for the destruction of the streptococcus; its action on the hands or vulva persists for several hours, and it has been in almost general use in maternity hospitals throughout Britain since 1934. It is used either pure or in a 30 per cent cream; and (10) the very thorough washing of the hands which was insisted upon in the no-glove era, has no doubt also proved effective as well as (11) the insistence on the wearing of masks by all attendants on the woman in labor or in the puerperium. The complete segregation of clean and possibly infected cases, which was possible in 1939, when the new Simpson Pavilion was opened, does not seem to have had such a beneficial effect as was anticipated, for it was only after two to three years' occupation that the morbidity rate decreased appreciably, the figures for the seven years after its occupation being 4.95 per cent, 5.86 per cent, 2.8 per cent, 4.1 per cent, 4 per cent, 2.9 per cent and 2.2 per cent.

TABLE VIII. MORTALITY STATISTICS FOR SEPSIS

	1926-30			1931-35			1936-40			1941-45		
	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE
Simpson	372	28	7.5	486	38	7.8	333	26	7.8	265	14	5.3
Glasgow R.M.H.	1517	59	3.9	2533	35	1.4	1120	34	3.0	901	35	3.9
St. Mary's	1072	26	2.4	989	19	1.9	571	14	2.4	582	14	2.4
Rotunda	433	18	4.1	465	15	3.2	498	18	3.6	617	5	0.8

TABLE IX. MORTALITY STATISTICS FOR ECLAMPSIA

	1926-30			1931-35			1936-40			1941-45		
	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE
Simpson	177	50	28.2	135	15	11.1	150	15	10 (B 5.4)	177	15	8.5 (B 3.4)
Glasgow R.M.H.	395	64	16.2	388	51	15	230	35	15.2	223	34	15.2
St. Mary's	174	17	9.8	129	18	13.9	89	18	20.2	94	10	10.6
Rotunda	60	13	21.7	55	8	14.8	55	9	16.4	86	10	11.6
Coombe	26	3	15.4	34	4	11.8	46	5	10.9	30	2	6.7

TABLE X. MORTALITY IN ECLAMPSIA AND PRE-ECLAMPSIA

	1926-30			1931-35			1936-40			1941-45		
	TOTAL DEATHS	PER- CENTAGE OF ALL DEATHS	PERCENT- AGE OF ADMIS- SIONS	TOTAL DEATHS	PER- CENTAGE OF ALL DEATHS	PERCENT- AGE OF ADMIS- SIONS	TOTAL DEATHS	PER- CENTAGE OF ALL DEATHS	PERCENT- AGE OF ADMIS- SIONS	TOTAL DEATHS	PER- CENTAGE OF ALL DEATHS	PERCENT- AGE OF ADMIS- SIONS
Simpson	64	33	0.59	30	17	0.26	28	20.2	0.2	17	20.5	0.09
Glasgow R.M.H.	107	20.4	0.52	77	17.3	0.31	49	15.3	0.2	41	15.2	0.18
St. Mary's	26	12.7	0.25	30	18.3	0.25	35	23.9	0.3	12	15	0.07
Rotunda	18	24.6	0.14	14	20.2	0.1	12	16.7	0.07	15	26.7	0.07
N. Y. Lying-In	19	14.1	0.11	3	10	0.02	1	2.2	0.002	Nil	Nil	

Toxemia

DeLee once stated that antenatal care had diminished the incidence of eclampsia, but, as far as the British hospitals are concerned, this reduction has occurred only in Glasgow and St. Mary's, and even they treated 223 and 94 cases, respectively, during the last five-year period. In fact, toxemia still accounts for a large proportion of maternal deaths, both in Britain and the U. S. A., as is shown in my tables. The New York Lying-In Hospital, however, again must be congratulated in so far as it reports only three deaths from toxemia during the last ten years, and none in the last five, and though the Chicago Lying-in Hospital gives almost as good results, yet the death rate from toxemia in 1941 for all the U. S. A. was 25 per cent of all maternal deaths. It is probable, therefore, that DeLee was not far out in his statement, as a large proportion of the cases of eclampsia come in as emergencies, when antenatal care has not been adequate. Only a few occur in patients attending antenatal clinics, and in these cases, the death rate is greatly lowered, viz. 4.4 per cent for booked, against 9.3 per cent for all cases of eclampsia at the Simpson for the last ten years. Be that as it may, the mortality is still appreciable, even in some districts where there is apparently adequate antenatal care. Theobald has pointed out that the incidence of eclampsia shows interesting geographical distribution which makes it difficult to compare different countries' statistics; even in a small country such as Britain, eclampsia is fairly common in the North, and relatively rare in the South. Though the general incidence of eclampsia has disappointingly not altered very much, there has been a decrease in the mortality rate in most of the hospitals, this being especially noteworthy in the Simpson and the Rotunda, whilst the number of deaths has been substantially decreased in Glasgow. This is partly due to improved antenatal care, but I believe that, as far as the Simpson is concerned, the improvement is principally due to the adoption of Stroganoff's method of treatment, and, in the last five years, to the more efficient isolation and nursing which were available in the new hospital, the mortality for this period being the lowest yet recorded, namely 8.5 per cent. At all the hospitals, the percentage mortality from eclampsia related to the total number of admissions has diminished for each quinquennial period, but this has little significance in Scotland, as the total number of cases of eclampsia admitted yearly has not decreased since 1930. These figures would seem to correspond with those of the Boston Lying-in Hospital, where the mortality rate from 1940 to 1944 was 13.5 per cent, which is definitely higher than the Simpson, and slightly lower than Glasgow. It was surmised that the reason there was practically no eclampsia in Germany during the final years of the 1914-1918 War, though it had been prevalent previously, was because the population was on a starvation diet and there was very little consumption of protein. It would seem that this conjecture is fallacious, as the protein available in Britain from 1942 was very small, and yet the incidence of eclampsia has not varied.

One cannot consider eclampsia, however, without also considering pre-eclampsia, eclampsism or profound toxemia without convulsions, call it what you will. If the mortality from eclampsia and profound toxemia are considered

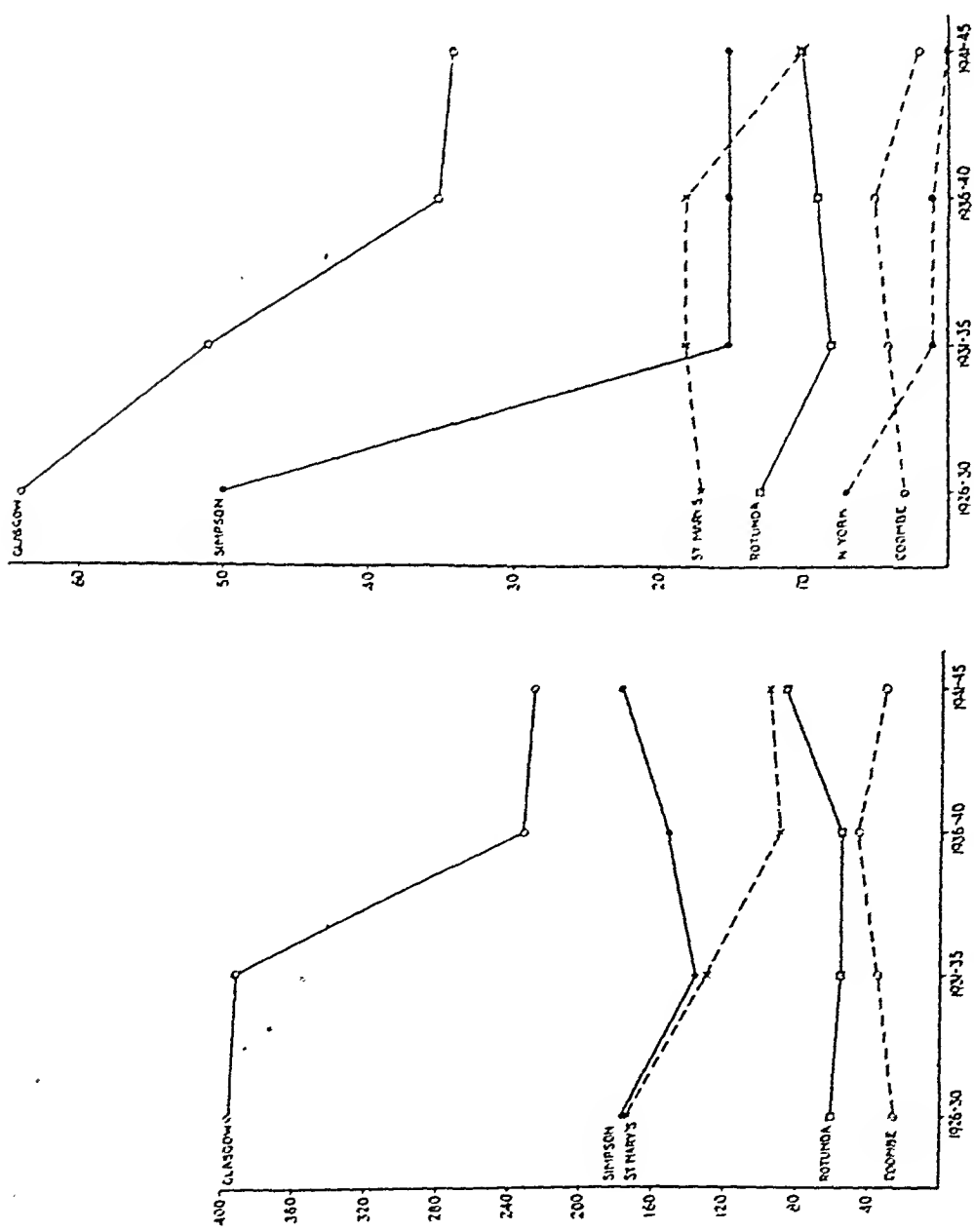


Fig. 6.

Fig. 6.—Eclampsia. Number of cases in five hospitals.
Fig. 6.A.—Eclampsia. Number of deaths in six hospitals.
Fig. 6.B.—Eclampsia. Mortality percentage of all admissions at six hospitals.

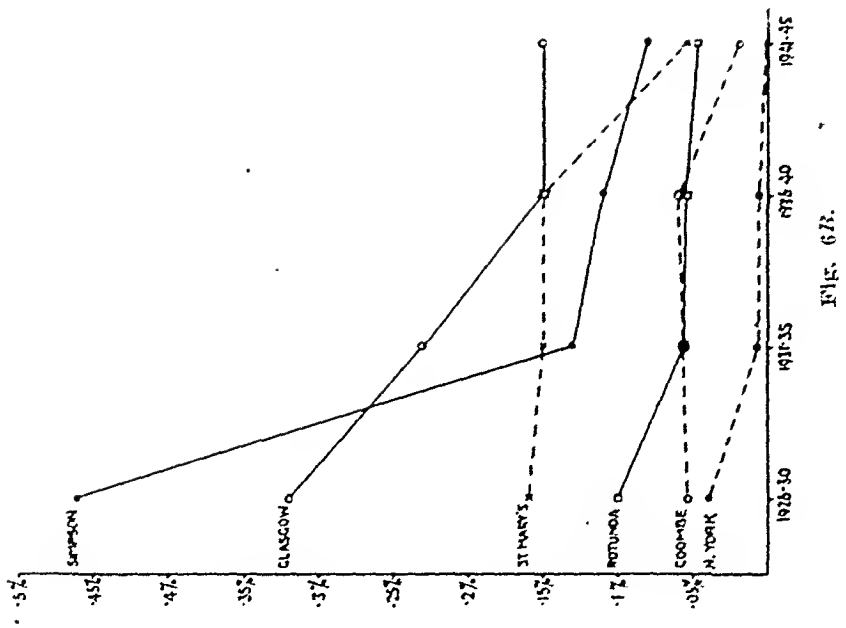


Fig. 6A.

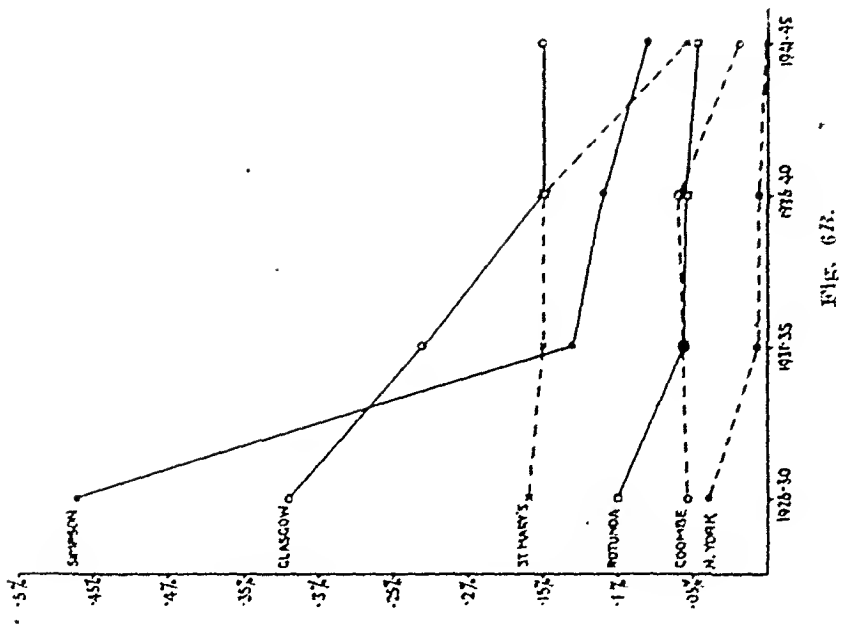


Fig. 6B.

together, it will be seen that the mortality has decreased very considerably in all the hospitals with the exception of the Rotunda, where the mortality has remained pretty stationary at about three deaths a year, which number is rather less than in the British hospitals quoted. In order to try and find a cause for this marked decrease in mortality, I have made a detailed study of the Simpson

TABLE XI. PRE-ECLAMPSIA

Mortality Rates and Treatments, The Simpson, 1926-45

	1926-30	1931-35	1936-40	1941-45
Cases admitted	627	712	1107	1592
Deaths	14	15	13	2
Percentage mortality	2.2	2.1	1.2	0.13
Percentage deaths for all admissions	0.13	0.13	0.08	0.01
<i>Treatments adopted—</i>				
Induction labor	125	317	514	672
Cesarean section	10	23	56	88
Abdominal hysterotomy	4	5	15	13
Induction abortion	4	7	7	2

statistics of pre-eclampsia during the twenty years, and it would appear therefrom that the principal reasons are: (1) the increased admission of pre-eclamptic cases, 1592 cases being admitted from 1941 to 1945, as against 627 from 1926 to 1931, due in the main to practitioners' appreciating the treacherous nature of pre-eclampsia and the value of hospitalization to permit of constant supervision, and also to the increased antenatal accommodation in the new Pavilion, which made this ideal feasible; and (2) the increasing number of pregnancies terminated by the induction of premature labor, cesarean section, or even abdominal hysterotomy during each successive five-year period. Eastman and Shieptoe have stated that everlasting vigilance and wary alacrity were necessary if pre-eclampsia was to be managed successfully, and Lazard recommended at the same time earlier termination of pregnancy to improve the results. These opinions are well corroborated by the Simpson figures, for, in the first five years, for 627 cases of pre-eclampsia, 125 labors and four abortions were induced and fourteen abdominal sections were performed, whereas, in the last five years, for 1592 cases of pre-eclampsia, 672 labors and two abortions were induced and 101 abdominal sections were done. By such treatments the mortality from pre-eclampsia has decreased from fourteen deaths (2.22 per cent mortality) between the years 1926 to 1930 to two deaths (0.13 per cent mortality) in the 1941 to 1945 period, and it is impossible to surmise how many cases of eclampsia were prevented. For comparison, Dieckmann reports seven deaths from Chicago during the same five-year period.

The mortality tables show very definitely that one toxemia, which gave great cause for anxiety in the past, namely hyperemesis gravidarum, does not cause the same concern now, Glasgow being the only hospital to show even an appreciable number of deaths during 1941 to 1945, namely seven. In the Simpson there has been no death from this cause during this last period and at St. Mary's there was only one death recorded; even in Glasgow, the total deaths from this cause have dropped from 38 in 1926 to 1930 to seven in 1941 to 1945.

Why has this occurred? From my experience in Edinburgh, I consider that it is due (1) to the early visit to a doctor or clinic, so as to get an extra ration book and clothing coupons, thus bringing the patients under observation much earlier than previously, and (2) to the better instruction of medical students

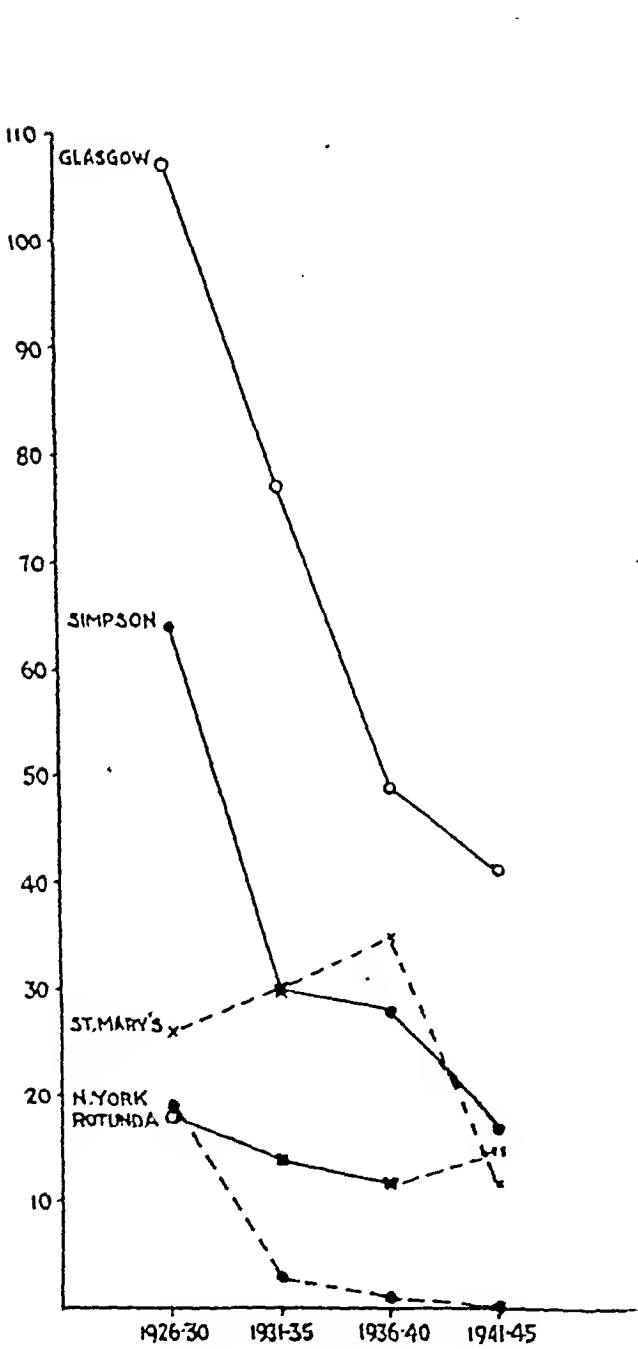


Fig. 7.

Fig. 7.—Eclampsia and pre-eclampsia. Total number of deaths in five hospitals.
Fig. 7A.—Eclampsia and pre-eclampsia. Mortality percentage of admissions.

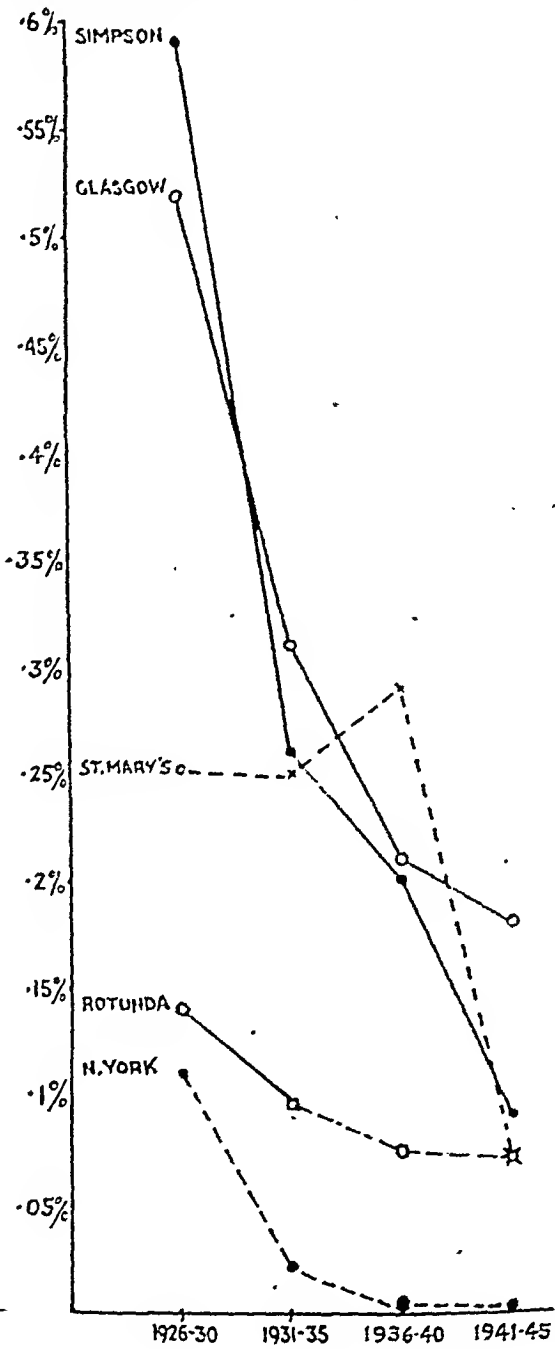


Fig. 7A.

as to the significance of vomiting in early pregnancy. They are taught to see their patients early in pregnancy, to inquire about nausea and sickness, and to treat it. If success does not follow domiciliary treatment, the patient is sent to hospital before serious symptoms develop. In the past, patients were seldom

seen early, and if nausea was complained of, this was often made light of by the medical attendant, and no treatment advocated; often, therefore, the patient was not treated adequately until the condition was far advanced. The Simpson statistics show this clearly, as there were 29 toxie cases of hyperemesis treated in 1926 to 1930 with twelve deaths, 43 in the next five years with eight deaths, 62 for the next five years with nine deaths, but only one toxie case was treated and that successfully during the War years. During this period, 130 cases of hyperemesis of moderate severity were admitted, as compared with an average of 290 for the other quinquennial periods. This diminution may also partly be due to the pregnant woman having had plenty to occupy her time and thoughts during the War years and thus the neurotic factor was to some extent eliminated.

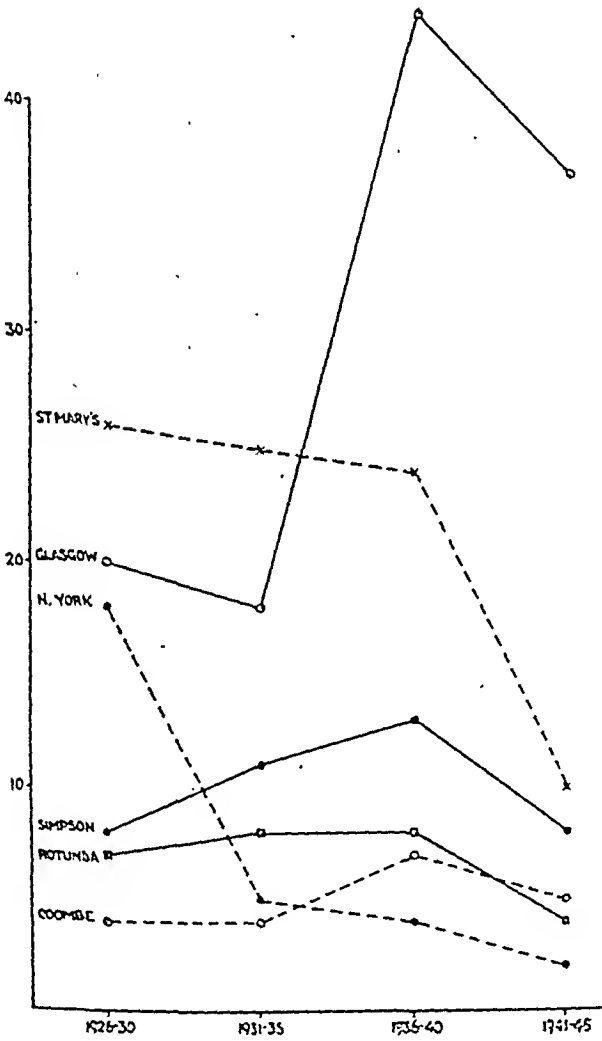


Fig. 8.

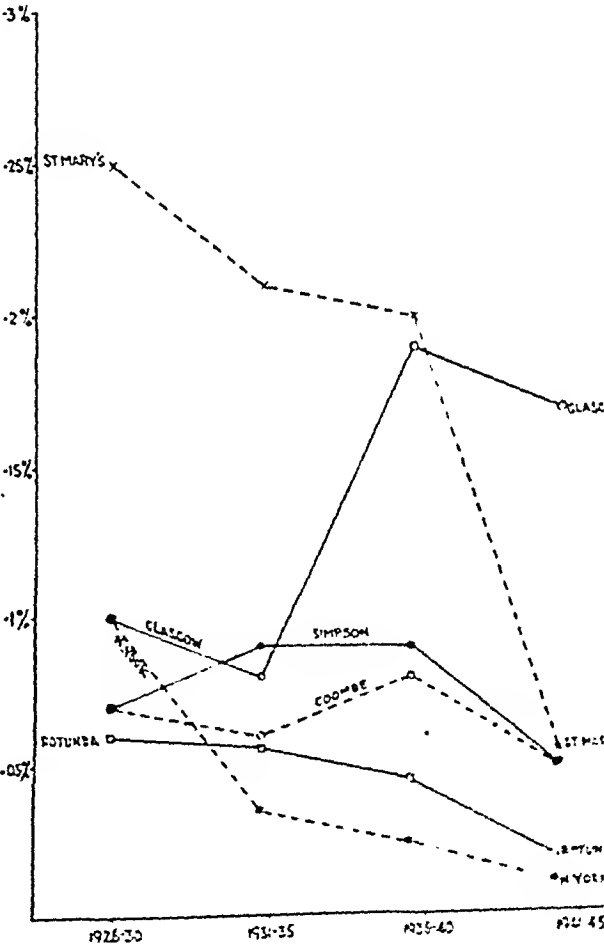


Fig. 8A.

Fig. 8.—Postpartum hemorrhage and shock. Number of deaths in six hospitals.

Fig. 8A.—Postpartum hemorrhage and shock. Mortality percentage of all admissions at six hospitals.

Hemorrhage

Under this heading I have included postpartum hemorrhage and obstetric shock, cases admitted after delivery outside with the placenta still in situ, which

TABLE XII. MORTALITY STATISTICS FOR PLACENTA PRAEVIA

	1926-30			1931-35			1936-40			1941-45		
	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE	TOTAL CASES	DEATHS	PERCENT- AGE
Simpson	189	12	6.3	208	11	5.3	214	8	3.9	235	2	0.9
Glasgow R.M.H.	419	52	12.4	490	31	6.3	504	12	2.4	413	12	2.9
St. Mary's	267	13	4.9	233	9	3.9	175	6	3.4	270	7	2.6
Rotunda	103	1	0.9	66	4	6.1	57	5	8.5	153	3	2.0
Coombe	47	8	17	65	5	7.7	81	6	7.4	89	2	2.3

TABLE XIII. PLACENTA PRAEVIA
Results of Principal Treatments at The Simpson

	1926-30			1931-35			1936-40			1941-45		
	TOTAL	MATER- NAL DEATHS	FOETAL DEATHS	TOTAL	MATER- NAL DEATHS	FOETAL DEATHS	TOTAL	MATER- NAL DEATHS	FOETAL DEATHS	TOTAL	MATER- NAL DEATHS	FOETAL DEATHS
Plugging with breech	111	6	88	78	9	72	38	2	34	31	0	24
Willet's forceps	2	1	0	36	1	17	46	0	29	47	1	16
Caesarean section	27	1	8	22	0	7	54	1	19	74	1	16
Combined Statistics for 20 Years												
	TOTAL CASES	MATERIAL DEATHS	PERCENT- AGE	TOTAL FOETAL DEATHS		PERCENT- AGE	TOTAL FOETAL DEATHS		PERCENT- AGE	TOTAL FOETAL DEATHS		PERCENT- AGE
Plugging with breech	258	17	6.6	218		84.5	144		72.2	104		72.2
Willet's forceps	131	3	2.3	63		48.1	100		32	32		32
Caesarean section	179	3	1.4	50		28.0	155		26	26		16.8

I have called retained placenta B.B.O. (baby born outside), placenta previa and, rightly or wrongly, accidental hemorrhage, some of which cases should better be classified under toxemia. By referring again to Table VII, it will be seen that for the British and Irish hospitals, with the exception of the Simpson, hemorrhage has caused the highest proportion of maternal deaths during the last ten years. In Glasgow this is partly due to the number of cases sent in after delivery outside with the placenta in situ, no fewer than 41 deaths being from this cause. This is not the case in the other hospitals, and no such case died in the Simpson from this cause during the last five-year period. Post-partum hemorrhage and shock account for 81 deaths in the Glasgow Maternity Hospital during the past ten years, being the principal cause of maternal mortality, and in St. Mary's they account for 34 deaths, also the principal cause of maternal mortality. In the Simpson, for the same period, the number of deaths from these two causes is 21 and is only the fourth most common cause of death. It is difficult to account for this high mortality, but it is probably due to (1) the admission of almost moribund cases; (2) the necessity for prolonged anesthesia for difficult deliveries for patients admitted as emergencies in far from satisfactory condition; (3) the large numbers of women who have borne 10 children or more who are admitted, whose uteri have lost their power of adequate contraction and retraction. It is possible that the comparatively new method of injection of ergometrine after the delivery of the head may cause a diminution of the number of deaths from this cause, but the treatment is still on its trial in Britain, and it is too early yet to be dogmatic regarding its benefits.

It will be seen from Figs. 9 and 9A and Table XII that the number of deaths from placenta previa has diminished considerably though the incidence of cases has remained fairly stationary. All mortality rates have decreased, and in the Simpson there have been only two deaths from placenta previa during the last five years, and they both occurred in the same year; this gives a mortality percentage 0.9 against 6.3 in the period 1926 to 1930. Can any reason be found for these satisfactory figures? I think it can, by considering the changes in treatment that have been adopted and which are demonstrated in Table XIII. In the earlier years, bipolar version, or plugging with the half breech, was the prevalent treatment and accounted for a high mortality rate, whereas, in the succeeding years, it was performed less and less frequently and the death rate improved. Contrariwise, cesarean section was carried out for only a few cases in the earlier years, but in the later years it was performed more and more frequently, and was associated with a low mortality rate. Also, in place of plugging with the half breech, with or without version, Willett's forceps came to be more frequently applied, having almost as low a maternal mortality rate as cesarean section. The use of Willett's forceps has been decried by some authorities and I have read many papers by United States authors deprecating their use; perhaps, therefore, I might be allowed to emphasize the good results that have been obtained by their employment in selected cases. As will be seen from my figures, the maternal mortality is low, though the fetal

mortality compares unfavorably with that of cesarean section. I would suggest, therefore, except in cases of marginal placenta previa, when rupture of the membranes alone suffices, if cesarean section is not indicated or advisable, that the application of Willett's forceps to the scalp of the child gives both mother and child the best chance of survival, and that there is a definite place in obstetrics for their use.

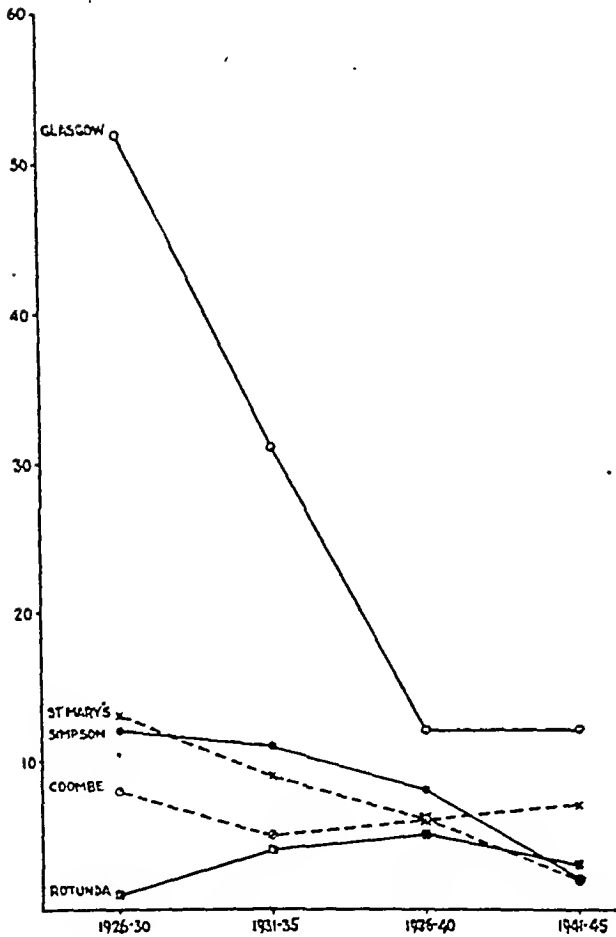


Fig. 9.

Fig. 9.—Placenta previa. Number of deaths in five hospitals.

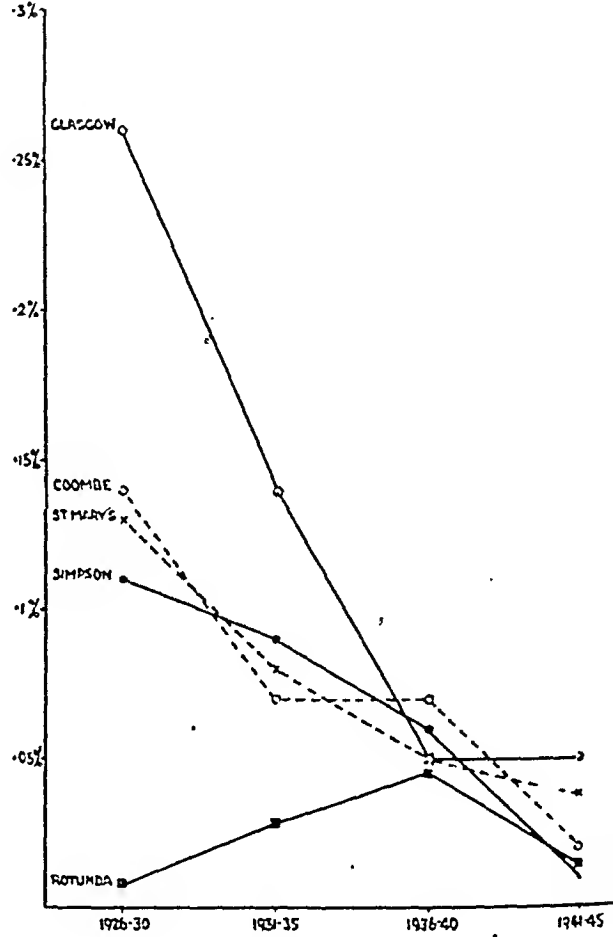


Fig. 9A.

Fig. 9A.—Placenta previa. Mortality percentage of all admissions at five hospitals.

In my opinion, the greatly lowered mortality in cases of placenta previa is due to three main reasons: (1) the adoption of cesarean section for the more dangerous types and the use of Willett's forceps, when indicated, in place of plugging with the half breech, (2) the almost routine use of blood transfusion as a prophylactic against the effects of possible dangerous blood loss and also as a replacement for any great loss, and (3) the fact that students have been taught that any case of bleeding in the last three months of pregnancy must have immediate hospitalization and be examined only by an expert; the high mortality in the earlier years was partly due to examination being carried out in the patient's house, excessive bleeding being caused and the patient being sent to hospital in extremis.

In some hospitals, notably in Glasgow, a number of cases are admitted with retained placenta, but these numbers are being diminished by the more frequent use of a flying squad of efficient personnel fully equipped with plasma and blood, so that the patients may be adequately treated in their own homes, and their condition rendered satisfactory before transportation to hospital. This again has involved the better instruction of students so that they are made to realize that the safest way to treat these patients is not to move them until shock and blood loss have been dealt with. It is pleasing to record that the Simpson, which provides such treatment, has had no deaths from retained placenta during the last five years.

The incidence of accidental hemorrhage as a cause of maternal death has diminished very considerably, the only hospital in which the mortality is appreciable from 1941 to 1945 being Glasgow, where they had fourteen deaths, whereas at the Simpson and St. Mary's, only one death was recorded at each. This improvement is again partly due to better tuition, by a better understanding of the pathology of the condition, and thus to more efficient treatment. Nearly all such cases are now treated expectantly, and cesarean section with or without hysterectomy, which used to be carried out frequently for the concealed variety, is now practically never required. The improvement is also due to the more efficient antenatal supervision of all cases of pre-eclampsia and especially those with marked hypertension. Thus once again a one-time dreaded disease can now be regarded with a degree of equanimity.

Failed Forceps Outside

Before discussing the future I would like to refer to another important cause of mortality in hospitals admitting non-booked cases, namely the so-called F.F.O.s—failed forceps outside—where the practitioner has tried to deliver with forceps, but, having failed to do so, sends the patient to hospital.

Quite an appreciable number of deaths in Glasgow, St. Mary's, and at the Simpson have occurred in such cases, especially where there had been gross interference before admission. The causes of death are shock, obstetric or anesthetic, sepsis, or, in a few cases, rupture of the uterus. The improvement achieved in dealing with such cases is illustrated in Figs. 10 and 10A. I consider that this improvement is due again to (1) better tuition of students, (2) more adequate antenatal care, so that cases likely to develop dystocia are recognized, and arrangements made for their delivery in hospital, and (3) improved methods of treatment in hospital, e.g., lower segment cesarean section, blood transfusion, anesthesia, etc.

What of the Future?

From the statistics that I have just put before you it will be appreciated that midwifery practice has improved in the last twenty years; the best results are obtained in the hospitals admitting few if any emergency cases, except from their own district cases, which latter are supervised by the hospital antenatal clinics. There is still room for improvement, especially in the standard of domiciliary midwifery without the aegis of the hospital antenatal clinics, so

that potential difficulties are recognized early and their unsuitability for domiciliary care realized; thus will serious emergency admissions decrease, and the few that are not foreseen will arrive in hospital in better trim and without trauma. How can this be achieved? This is a very important consideration and especially so is it in Great Britain, where we are approaching a new era in the practice of medicine, with the advent of a National Health Service, which includes midwifery and is due to start on July 5, 1948. It is the duty of the obstetricians therefore to advocate a scheme, which, if carried out efficiently and conscientiously, will give Britain, despite its large and crowded industrial centers, a chance of producing the lowest mortality, morbidity, and infant mortality rates in the world. My suggestions for future improvement are as follows.

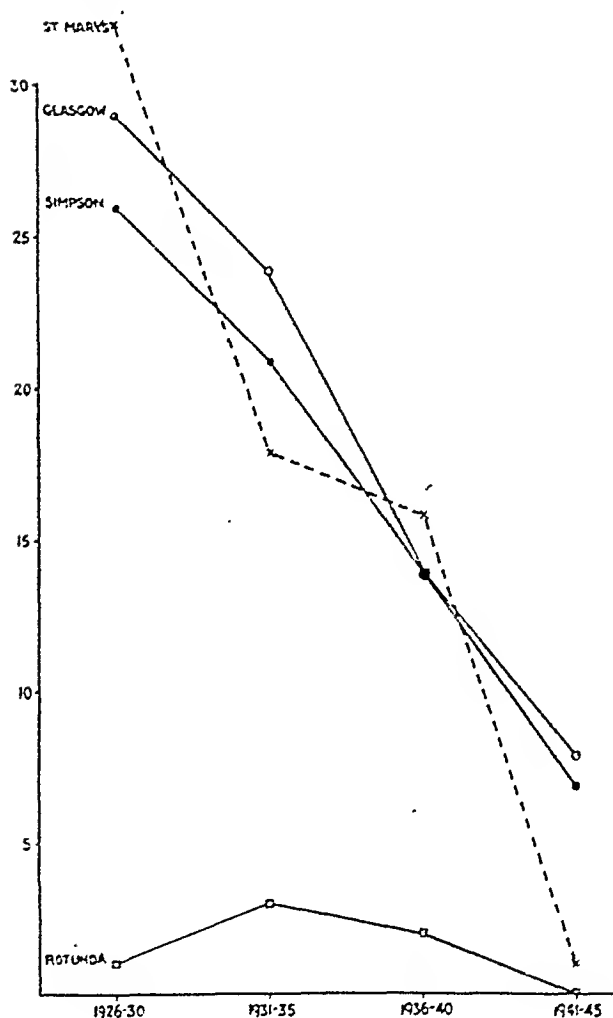


Fig. 10.

Fig. 10.—Failed forceps outside. Number of deaths in five hospitals.

Fig. 10A.—Failed forceps outside. Mortality percentage of all admissions at four hospitals.

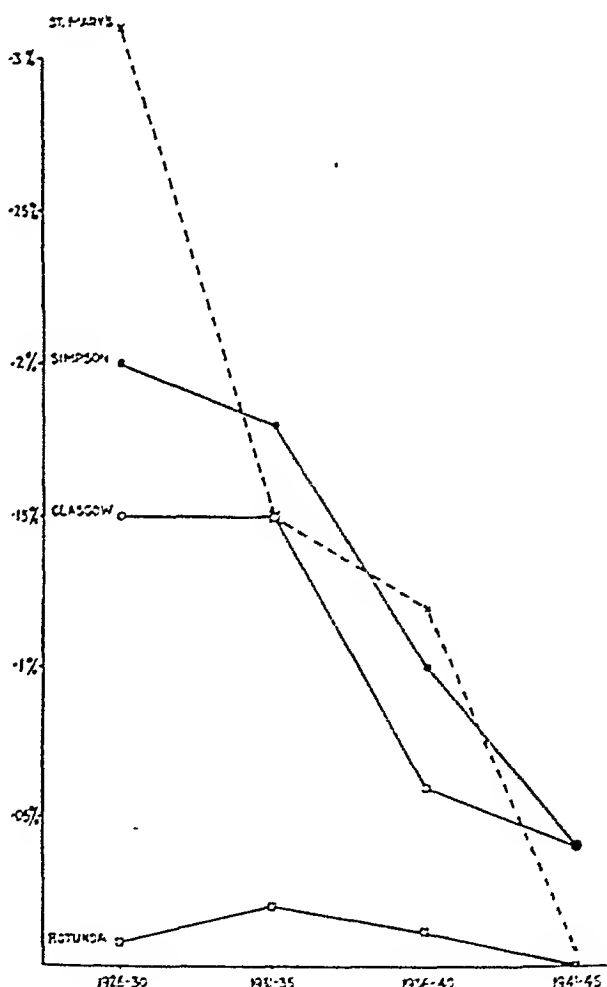


Fig. 10A.

Adequate and Efficient Antenatal Care for All Pregnant Women

The importance of efficient antenatal care can be gauged by noting the disparity between the mortality percentage amongst the booked cases, i.e., those who have attended at least two antenatal clinics (a very low criterion) and the total mortality percentage of all cases admitted both booked and unbooked as

already remarked upon (shown for the Simpson in Fig. 2). The statistics of the New York Lying-In Hospital would seem to afford an excellent example of how efficient antenatal care for the hospital and surrounding district can lower the mortality to almost an ideal minimum.

Though antenatal care has progressed out of all knowledge during the last thirty years, it is still far short of being ideal, and I would suggest that improvement could be achieved under the following headings:

(a) *Personnel*: The responsibility for antenatal supervision must devolve on those with some extra postgraduate training in midwifery, which experience alone can make them conversant with its numerous problems and pitfalls. The undergraduate standard of instruction is only sufficient to permit of practice under supervision.

(b) *Antenatal Clinics*: The large clinics, which are so common in Britain at present, owing to the increasing number of antenatal patients, should be abolished. What clinic can see and examine efficiently 200 or more patients in an afternoon? These clinics should be more individual, the patient being seen by the same doctor at each visit, so that each case can be followed up satisfactorily, and a personal interest taken. This would greatly help the patient's comfort and confidence and would be advantageous when slight abnormalities, which might escape notice by a new examiner, made their appearance. No session should be longer than two and a half hours and no individual doctor should undertake the examination of more than 25 cases in that time.

(c) *Accommodation*: There must be adequate antenatal in-patient accommodation, with (1) sufficient nursing and medical personnel for all patients requiring hospital supervision and treatment, such as those suffering from toxemia, cardiac disability, diabetes, antepartum hemorrhage, pyelitis, or mere debility, etc. The first antenatal bed in the world was provided at the old Simpson Memorial Hospital in 1899 by one of your Honorary Fellows, the late J. W. Ballantyne, the pioneer in antenatal care, but it was not until 25 years later that an antenatal ward came into existence, and it had only ten beds. When the new Pavilion was erected in 1939, it was thought that 25 per cent of the total beds should be devoted to antenatal cases, and approximately 30 beds were given over for such cases. This has been found to be entirely insufficient and it would appear that about 40 per cent of the total beds in a maternity hospital should be devoted to antenatal cases, the exact proportion depending on the character and working conditions of the population in the area which the hospital serves. (2) Sufficient lying-in accommodation must also be provided for all cases regarding the difficulty of whose confinement there is any doubt. This would include all primiparas and multiparas who had had nine previous confinements, besides patients with slight contraction of the pelvis, with history of previous difficult labors or stillbirths, etc.

Teaching

There must be more practical and clinical training of students or of young graduates, who are going to undertake midwifery in their general practice.

I agree wholeheartedly with H. M. Little, who, in his presidential address

to the Canadian Medical Association in 1924 on the Progress of Obstetrics in the preceding 25 years, stated, "Antenatal care by itself is hopeless without some improvement in the teaching and practice of obstetrics. The most recent graduate is no more capable of undertaking any but the simplest midwifery cases than he is to practice abdominal surgery," and concluded by advocating better training for students and special training for men in large centers, who aim at becoming specialists. Undergraduate training in midwifery in Britain has made great strides in the last twenty years, but the average graduate is still allowed to go into general practice badly equipped in practical experience though his theoretical knowledge may be satisfactory.

I would suggest, therefore, that every doctor who wishes to make midwifery part of his general practice and will therefore be undertaking antenatal examinations should have three to six months' intensive experience in practical midwifery, including antenatal and postnatal care, residing in a maternity hospital, before he is allowed to practice midwifery. An extra degree, such as a B.Obst. or B.A.O., could be given to these graduates, which would give proof of their experience and status to practice general practitioner midwifery. This would ensure not only that efficient antenatal care would be afforded but also that the practitioner would be able to recognize and assess the severity of abnormal conditions occurring during labor; he would realize if a condition was beyond his resources or capabilities and would send the patient to hospital early, not interfered with and in much better trim, and without trauma. Thus the failed forceps case, instead of being a common cause of mortality, would become more and more a relic of the past, and many lives would be saved thereby.

Compared with these two fundamental factors, my other suggestions are of minor significance, but I think if practiced would aid the progress of midwifery.

Blood Grouping

Every pregnant woman should be blood grouped and her Rh factor taken. This would seem to be as important, if not more so, than the routine Wassermann reaction. Such a procedure would save fatalities following transfusion which, unfortunately, are by no means rare, and would also accelerate reliable transfusion in urgent cases.

Flying Squads

Flying Squads, fully equipped, should be immediately available night and day in order to deal with cases of hemorrhage and shock and retained placenta occurring in the area served by the hospital and should be at the service of all practitioners in that area who required their aid. As has been already noted, this would save a number of lives and prevent cases being transferred to hospital in a collapsed and often moribund condition.

Hospital Construction and Administration

Besides adequate accommodation already mentioned for antenatal cases, there must be efficient administration to prevent the spread of any infection in the hospital: (1) Patients should be delivered each in a separate room, and

the big labor ward, which was once so common, must be abolished. (2) Emergency cases admitted during labor must be isolated efficiently from the so-called booked or clean cases; they should be delivered in entirely separate labor rooms, which should be disinfected after each case, and if single rooms are not available for all such cases for the puerperium, the wards should have few beds and be well-aired; there should be, however, sufficient single rooms for the frankly or likely septic cases. (3) There should be an entirely separated ward, or preferably, block for cases of abortion; they should be completely isolated from the puerperal patient whether clean or suspect, and their treatment should be carried out in a separate theatre. This has been rarely possible in Britain, and the admission of abortions to maternity hospitals, besides often raising the mortality rate, may be a potential cause of increased morbidity.

Penicillin and Possibly Other Therapeutic Agents

Great improvement has been effected in lowering the morbidity rate and the number of deaths from sepsis by efficient technique and hospitalization and by the administration of the sulfonamides, both prophylactically and curatively. What further improvement may follow the extended use of penicillin? It is as yet too early to speak definitely on this point, but the prospect seems hopeful. Also, may there not be some new preparation round the corner, soon to be discovered, which may prove to be even more potent than either? And, last, what a niche in obstetric history awaits the man or woman who discovers the cause of pre-eclampsia and eclampsia, for once the cause is discovered, specific treatment or, better, the knowledge of its prevention will surely follow at no far distant date, and another common cause of maternal mortality will be conquered.

BENIGN TROPHOBLASTIC CELL PROLIFERATION*

C. G. TEDESCHI, M.D., AND A. A. MATARESE, M.D., FRAMINGHAM, MASS.

(From the Laboratory Department and the Department of Obstetrics,
Framingham Union Hospital)

WHENEVER an invasion of the uterine wall by trophoblastic tissue occurs, two possibilities may be present: benign trophoblastic cell hyperplasia or a form of chorionepithelioma. Since differentiation between the two conditions is based quite often on a matter of opinion rather than definite histologic criteria, many uteri are sacrificed needlessly.

Many observers have noted that trophoblastic cells may invade the uterine wall in normal gestation. According to Marehand¹ the process is not a casual one, but it serves the purpose of firmly anchoring the implanted ovum to the uterine wall. The amount and extent of this cellular infiltration vary considerably; it increases up to the sixth month, to disappear almost completely toward the end of pregnancy. In only a small number of cases, the infiltrating cells invade the blood vessels, with subsequent formation of pulmonary emboli. Sehmorl² found that this occurred in 80 per cent of 150 eclamptic cases studied at autopsy. His conclusions were based on the presence of scars in the pulmonary tissue which he claimed to be the end result of absorption of previous trophoblastic cell emboli.

Moreover, many authors who have examined uteri with adherent moles or placental tissue have remarked on the amazing depth of invasion of the villi into the uterine musculature. The early literature lists this finding under the term of placental polyp. It has been suggested that the aggressive tendencies of these trophoblastic cells are kept in check by a restraining factor, synectiolysin, which is produced by pregnant uterus. In favor of this mechanism, Frankl³ has shown that the serum of normal pregnant women has solvent properties on these embryonal cells in vitro; the serum from pregnant women with chorionic epithelial tumors does not contain this solvent action. Other observers have not been able to demonstrate this synectiolysin. Of late it has been thought that a disturbed lutein function accounts for the excessive trophoblastic growth.

As far back as 1898, Ruge⁴ stressed the point that as long as the chorion-epithelial cells (at his time interpreted as of decidual origin) are still connected with the villi, it is proper to speak of proliferation and not of new growth, the latter term implying a kind of independent cellular life. This conception of independent life and aggressiveness which applies to any cellular proliferation elsewhere in the body does not apply, however, to the growths under consideration, invasiveness and obliteration of neighboring structures being inherent to the normal implantation of the ovum into the uterine wall. The absence of a sharp line of demarcation between normal and pathologic growths requires special notice, because it is just in border-line situations that difficulties may arise. These difficulties are clearly reflected by the disparity that still exists in the statistics on the actual frequency of chorionepithelial growths.

Velits⁵ is credited with the first attempt to differentiate chorionepithelial cell proliferation into a benign and a malignant form utilizing histologic criteria. The absence of mitotic figures, the predominance of wandering cells, and extensive tissue necrobiosis—these factors were indicative of the harmless growths. In actual practice, this information could not be obtained unless the uterus was already removed.

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More important progress was made by Marchand¹ who, in a series of articles from 1895 to 1903, was able to demonstrate that the "deciduoma malignum" of Sanger was derived from chorionic epithelium, from which both typical and atypical growths might occur. Typical chorionepithelioma he called that characterized by the presence in varying proportions of small, polyhedral, pale-stained cells with intimate cytologic characteristics of Langhans' cells and of large multinucleated plasmodial masses simulating the syncytial buds of the villi, these two cell types together giving rise to a well-defined structure closely resembling the epithelial cover of villi in early stages of placentation. He termed atypical chorionepithelioma that in which the Langhans' cells were missing and only giant syncytial cells could be recognized in the growth. Although Marchand did not claim any striking difference in the clinical course between the two types of growths, the typical and the atypical, a few years later Schmauch,⁶ after careful review of 206 cases, concluded that Marchand's atypical forms were provided with much less aggressive potentialities than the definite malignant forms. He also recognized a transitional type, of intermediate malignancy, "composed chiefly of elements like syncytial cells, assembled in groups, as well as syncytium and Langhans' cells." According to Schmauch, while, in the typical forms, the structural patterns compared with those found in early stages of pregnancy, in the atypical ones they resembled more closely those found in the puerperal uterus. In his opinion, prognosis depended mainly upon the abundance of the most aggressive cellular type, the cell of Langhans. This assumption was based on Langhans' theory that the chief part in the embedding of the villi was played by the Langhans' cells, not by the syncytial cells as thought by Marchand; hence, his conclusion that the more numerous the Langhans' cells, the worse the prognosis; conversely, whenever evidence of syncytial change in the Langhans' cells and of transformation of syncytium in the syncytial cells prevailed in the growth, the outlook for the case was more favorable.

Schmauch paved the way for Ewing's⁷ masterful study of the problem. Although not denying that the syncytial wandering cells of the atypical chorionepithelioma of Marchand are capable of multiplying, Ewing considered it unlikely that these cells could be able to develop into a progressive malignant tumor. After stressing the point that definite syncytium, Langhans' cells, and villi are missing in the growth, and that the cases exhibiting budding syncytium and Langhans' cells must be rigidly excluded from the group under consideration, he concluded that the so-called atypical chorionepithelioma was a "productive inflammation," a "mixture of degeneration with proliferation" accompanied by thrombosis of blood vessels and tissue necrosis; hence his proposal to term the process "syncytial endometritis," clearly indicating the true essence and harmless nature of the process.

For another type of transitional lesion in the chorioma group, he proposed the term "syncytioma or syncytial chorioma." This tumor is not made of just isolated cells, as in syncytial endometritis, but is composed of sheets or masses of giant syncytial wandering cells. Langhans' cells might be present in this type of growth, but they are an inconspicuous feature, and they fail to reveal any evidence of hyperplastic or anaplastic tendencies. Instead, the wandering cell plays the role of invader, but capable of producing a tumor of only limited aggressive potentialities. This tumor progresses for a while, then loses its power of further expansion, and then undergoes a process of regression.

This work of Ewing sheds considerable light on the so-called cured cases of chorionepithelioma previously reported in literature. Velits⁵ collected eight cases of chorionepithelioma which completely recovered after eurettage. More likely these were cases of syncytial tumors of Ewing rather than true chorionepithelioma. The same is probably true of the two cases of Proust and Bender,

those of Noble, Fleischmann, Cazin-Segond, Kolomenkin and Hormann (discussed in Ewing's paper), and more recently of the nine cases of Vineberg,⁸ eight of which completely recovered following hysterectomy. The latter attributed his excellent results to early diagnosis, but one wonders if they did not belong to the syncytial group. Rosenzweig⁹ raised the same question in the chorionepithelioma reported by Ferguson.¹⁰

In line with Ewing's nomenclature, Geist¹¹ has reported four cases; two belong in the "syncytial endometritis" group and two in the "syncytioma" class. Similarly, Rosenzweig has reported one case in each group. The three cases of Greenblatt and Pund,¹² each exemplifying a condition of syncytial endometritis, syncytioma, and of exaggerated syncytial reaction following an abortion, were so diagnosed and treated conservatively. A case similar to the last one of Greenblatt and Pund was reported by Choisser and Notes.¹³ They attributed the endometrial reaction to the combined effects of hyperestrinism, low-grade infection, and to trauma produced by the long-continued use of a metal-stem pessary.

In the series of 200 cases of hydatidiform mole collected by Hertig and Sheldon,¹⁴ nine were diagnosed as "syncytial endometritis." They placed them in Group VI among the malignant moles. They were placed in the malignant mole group because of the invasive character of the trophoblastic cell proliferation. Yet, of these nine cases, two patients were alive and well seven months and four months, respectively, with their uteri intact after removal of the mole only. Of the other seven, submitted to hysterectomy, one died postoperatively of peritonitis, and the remaining six were all alive and well three months to nine years later. It is apparent, as the authors pointed out, that these nine cases, despite their threatening morphologic structure, did not constitute a true chorionic malignancy. These authors also present another case, that of a woman who passed a mole which appeared to be malignant upon microscopic examination. A curettage done on the sixteenth postpartum day yielded a few myometrial fragments from the placental site, displaying patterns consistent with a diagnosis of syncytial endometritis. A hysterectomy was advised but refused by the patient, who, after four years, is still living and well. This and other similar cases show that the usual morphologic criteria of malignancy universally observed in grading tumor growth are not strictly applicable to trophoblastic cell proliferation.

In light of the above experiences it becomes apparent that only through the follow-up of cases carefully studied pathologically can proper evaluation be gained in ascertaining the necessary operative interference.

Report of Cases

CASE 1.—The patient, a 22-year-old white woman, was admitted to this hospital with a history of vaginal bleeding of two days' duration, which had started after a two months' period of amenorrhea. She had always had regular menses, with no bleeding in between periods. Family and past history were irrelevant. Examination at admission revealed a well-nourished young woman. Findings in the chest and abdomen were completely negative. A vaginal examination was made, and it revealed a patent, softened cervix from which a good deal of blood was issuing. The impression was of a threatened miscarriage and, as bleeding was continuing, a curettage was performed.

At curettage, the surfaces of the uterine cavity were found to be somewhat thickened and lined by a firm tissue, grayish-pink in color, which did not have the usual gross characteristics of placental tissue.

Microscopic examination of the curettings showed a thickened endometrium, spongy in appearance, due to marked hypertrophy and tortuosity of glands. The latter presented pronounced saw-tooth convolution and scalloping, and were lined by a low, pale-stained and

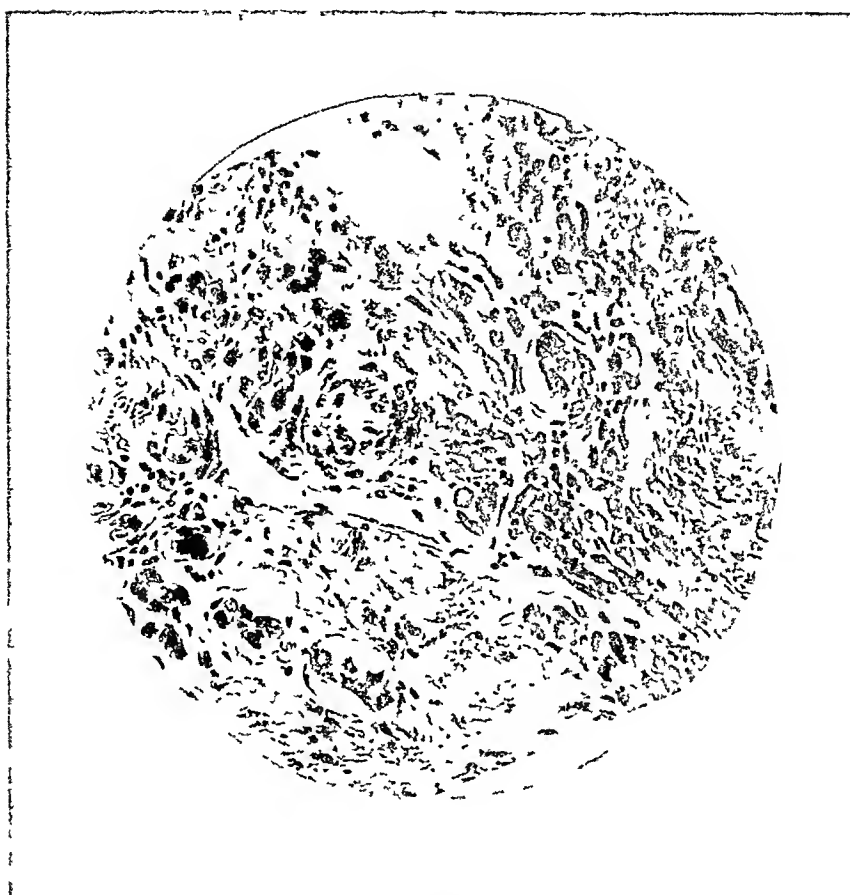


Fig. 1.—Deep invasion into the myometrium of atypical trophoblastic cells, either sparse or in large sheets. Cells identical in type are noticeable in the lumen of thin-walled hematic channels. (Case 1—Microsc. Zeiss—Oc. 10—Object 10.)

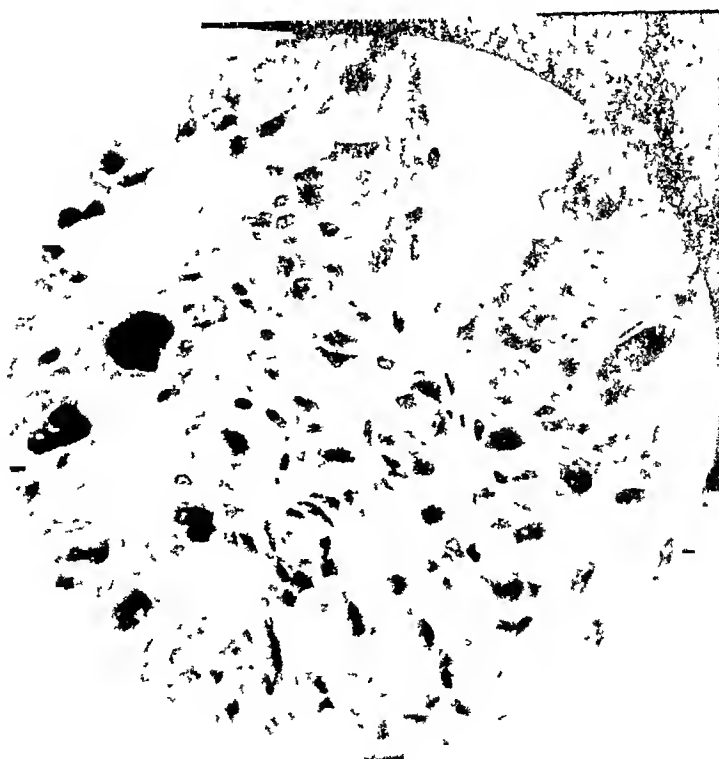


Fig. 2—Oddly shaped, deeply stained, not distinctly bounded trophoblastic cells infiltrating the myometrium. (Case 1—Microsc. Zeiss—Oc. 10—Object 46.)

actively secretory epithelium with a frayed-looking edge suggesting melting-down of cytoplasm. The superficial endometrial layers showed patchy necrobiotic changes, with poor staining of cellular structures and imperfect cell differentiation. A rather massive infiltration of leucocytes, chiefly polynuclear, numerous mononuclear clasmatocytes, and a good many extravasated red blood cells were noticeable in these degenerated areas, together with interglandular stroma extremely rich in cells, which were larger than the usual endometrial stroma cells, round or polygonal in shape, with a wide zone of cytoplasm surrounding the nucleus. These cells, with characteristics of decidual cells, were arranged in mosaic-like fashion and appeared to be most numerous where the glandular elements were few.

Elsewhere a few chorionic villi were recognizable; they seemed to have undergone advanced regressive changes, as shown by the poor staining and imperfect cell differentiation, with partial or complete hyaline degeneration. The epithelial covering of the villi was missing in some areas, hyperplastic in some other areas. Where the structure was better preserved, it appeared to be composed of cells of various size and shape, some large and some small, some polyhedral, some others round or elongated or bizarre-shaped. All these cells were characterized by a deeply stained, irregular nucleus surrounded by abundant acidophilic cytoplasm. Cells identical in type, either sparse or in large sheets, were scattered in the decidual tissue and deeply infiltrated fragments of myometrium obtained at curettage. (Fig. 1.) The cells within the myometrium showed a tendency to fuse together into plasmodial masses, and as they fused together, the nucleus and the cytoplasm stained deeper, and in their coloring and structure they resembled syncytial cells. In other areas these cells grew to gigantic proportions, giving rise to oddly shaped, deeply stained and not distinctly bounded cells which were especially numerous in the proximity of thin-walled intramyometrial blood vessels. (Fig. 2.) Cells identical in type were noticeable at times in the lumina of the vessels themselves. As these cells penetrated in the depth of the myometrium they seemed to lose the polyhedral or round shape that they displayed in the decidual tissue and often assumed a spindle form, so that it was difficult to differentiate them from connective tissue cells, the fundamental difference being their greater affinity for stains. Despite the evident cellular aggressiveness, with invasion of blood vessels, deep infiltration, and spreading apart of muscular fibers, no mitotic figures could be recognized. The intervening muscular structures showed patchy regressive changes with loss of striations and hyaline changes which increased in severity with the increase of the cellular infiltration.

Our final impression was that the picture was not unlike that ascribed to the so-called atypical chorionepithelioma. The provisional diagnosis was syncytioma, but, as we were undecided as to real malignancy of the process, a decision was made to treat the patient expectantly.

Following curettage, two gonadotropic hormone tests were performed two weeks apart and both yielded negative results. At the end of one month a second curettage was done, and, amazingly, the general appearance was found to be that of a normal endometrium in the secretory stage of the menstrual cycle. No plasmodial cells or any other structural or cellular atypism could be recognized, and the fragments of myometrium obtained at curettage were found to be free from cellular infiltration. The patient made an uneventful convalescence and she is now perfectly well, and in the fourth month of a normal pregnancy.

CASE 2.—The patient, a 19-year-old white woman, was admitted to this hospital with a moderate amount of vaginal bleeding, which, according to the history, had started about two months before and since then had persisted off and on, after a two months' period of amenorrhea. During this period she had noticed swelling of the breasts, and had suffered with frequency and nausea. The family and previous personal history were irrelevant.

Examination on admission showed a well-developed and well-nourished young woman with no physical complaints except for the vaginal bleeding. Vaginal examination revealed an enlarged uterus, about the size of a two and one-half to a three months' pregnancy. The external os was completely closed. The patient was kept four days under observation, with no particular treatment except bed rest. The bleeding quieted down somewhat, so that, on the fourth day, she was discharged, with the advice that she should return if bleeding should start again. Diagnosis on discharge was threatened miscarriage, probably inevitable.

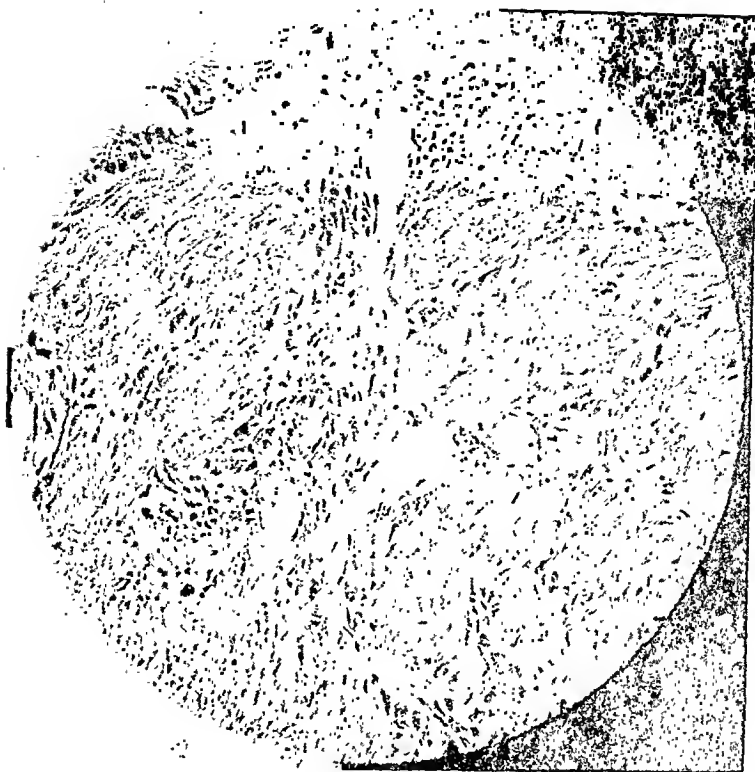


Fig. 3.—Large sheets of cells with characteristics of Langhans' cells and occasional larger cells in syncytial arrangement infiltrating and spreading apart the muscular bundles of the myometrium. (Case 2—Microsc. Zeiss—Oc. 10—Object 10.)



Fig. 4.—A view at high magnification of the infiltrating trophoblastic cells represented in Fig. 3. (Case 2—Microsc. Zeiss—Oc. 10—Object 40.)

She was readmitted 22 days later with a slight amount of vaginal bleeding and intermittent abdominal cramps. The day of admission she passed a fetus, two inches in length, and some shreds of placental tissue. A curettage yielded abundant soft tissue, grayish-pink in color, interspersed with a generous amount of freshly coagulated blood.

Microscopic examination of the curettings showed a thick endometrium, markedly spongy in appearance, due to the presence of numerous dilated, irregularly shaped glands lined by a secretory epithelium of the lutein phase. The interglandular stroma was edematous, hemorrhagic, and showed a diffuse infiltration by decidual cells. Necrobiotic changes were present in places and, in these areas, numerous granulocytic cells and thrombosed blood vessels were present. Elsewhere chorionic villi were recognizable. Some showed advanced retrogressive changes, while others were still well preserved and displayed pluristratification, in irregular fashion, of trophoblastic cells. Among the latter, cells with characteristics of Langhans' cells prevailed and only a few syncytial cells were noticeable here and there. The striking finding, however, was that of large, oddly shaped, deeply stained cells which did not resemble either the Langhans' or the syncytial or the decidual cells. These large cells showed great variations in size and shape, nuclear giantism, at times two or three nuclei, but, even in the thinnest microscopic section, due to pronounced hyperchromatism, no nuclear details could be made out, and, as the cytoplasm also was deeply stained, the limits between nucleus and cytoplasm could not be seen distinctly. Cells, identical in type, either scattered or in clumps, were found also at a distance from the chorionic villi, in the interglandular endometrial stroma, and in fragments of myometrial tissue obtained at curettage. (Fig. 3.) As the cells penetrated in between the muscular fibers, they showed a tendency to assume an elongated or spindle shape and to fuse together with loss of boundaries and of cellular outlines. (Fig. 4.) This resulted in the formation of plasmodial masses which appeared to be most numerous in the proximity of thin-walled blood vessels. No actual invasion of blood vessels could, however, be detected and mitotic figures were never seen among the proliferated cells.

In this case also, the impression was an atypical trophoblastic cells proliferation, perhaps less severe than in the previous case, and fitting in the category of the so-called syncytial endometritis. The course of the process was closely followed with frequent gonadotropic hormone tests. After two months they were still negative, and after a nine-month interval the patient is in excellent health.

Comment

If the criteria usually advocated in the differentiation between a hyperplastic or a dysplastic cellular growth elsewhere in the body had been applied to the patterns observed in the two cases under consideration, the final judgment might have been that of a malignant process, and the process treated accordingly; but it has been already known that the criteria of malignancy in the cellular growths elsewhere in the body do not apply directly to this particular type of uterine growth. In the discussion of Hertig and Sheldon's paper, this point has been stressed by Novak.¹⁵ Since invasiveness, with consequent obliteration of neighboring structures, is a quality inherent to the trophoblast under normal conditions, it is obvious that we must turn our effort to the detection of other criteria in trying to evaluate the nature of the process.

Amount and depth of the cellular infiltration of course are important, but obviously cannot be considered the decisive criterion, since deep penetration of trophoblastic cells in the uterine wall is said to occur in the normal pregnant uterus.

More valid information, in our opinion, can be obtained by the careful study of the cytologic characteristics of the cell type mainly involved in the proliferative process. In our two cases, as in the cases of others, variously

interpreted as atypical chorionepithelioma or syncytial endometritis or syncytioma, the role of the invader was played mainly by large, round, polyhedral or bizarre-shaped cells with hyperchromatic nuclei and slightly acidophilic cytoplasm. These cells showed a tendency to enlarge to gigantic proportions, the enlargement being due mostly to swelling of the nuclei; and, as the cells enlarged, the nuclei became further hyperchromatic and displayed evidence of karyorrhexis and karyolysis, signs of impending cell dissolution. Mitotic figures were not seen in our two cases and very rarely were mentioned in the description of similar cases by others.

A number of terms, such as wandering cells, chorionic wandering cells, chorioectodermal syncytial wandering cells, syncytioblasts, puerperal cells, unknown cells, have been proposed for these types of cells, which older writers regarded as decidua cells, and which most of the modern authors consider of fetal origin. The different names proposed are indicative of the lack of agreement among the authors on the nature and significance of these cells. Among the terms proposed, "syncytial" has been accepted, due to the strong resemblance of these cells to the syncytial cells of the epithelial covering of the villi. Schmauch⁶ and Greenblatt and Pund¹² found them to resemble decidua cells. We often received the same impression but one cannot judge on pure resemblances. According to Schmauch,⁶ these cells do not originate from the syncytial cells, but from the "finest sprouts" of the Langhans' cells, which have undergone a plasmodial change. Greenblatt and Pund¹² have coined the term "metasyncytium" for these "plasmodial ribbon-like masses" which, in their opinion, are derived from and appear to be a later stage of Langhans' cells.

Regardless of the discrepancies that still exist as to the origin of these cells, all authors agree that the "plasmodial pattern" represents a form of reduced vitality of the trophoblast. Ewing⁷ has made this clear when he first employed the term of syncytial endometritis to replace Marehand's atypical chorionepithelioma. The presence of cells of identical character in regressing hydatid moles, degenerating chorionata, destructive moles, placental polyps, and around necrotic villi is further evidence of the retrogressive character of these plasmodial masses, for which it might be proper to speak of "hypertrophic degenerated trophoblastic cells." Rosenzweig⁹ also is against the neoplastic nature of these cellular structures, and the same opinion is advanced by Greenblatt and Pund¹² and by Choisser and Notes.¹³ A number of reports in the literature claiming spontaneous recovery of chorionatous growths seem to justify Ewing's contention that the trophoblastic cells can carry aggressive tendencies for a while, then lose their developing power, and finally undergo a process of reduction.

While the harmless nature of our two cases is clear, it is difficult to explain the stormy proliferation and invasion by trophoblastic cells which preceded their regression. Loss of "restraining factor" might be an explanation, but, in our opinion, the existence of a "syncytiolysin" is not demonstrated convincingly enough. Hormonal dysfunction is another possibility, but again we are in the field of the hypothesis, difficult to prove. Necrobiotic hemorrhagic changes, thrombosis of blood vessels, and diffuse infiltration by inflammatory cells were outstanding findings in both our cases, and they have been emphasized

in a number of similar cases reported in the literature. Perhaps local disturbances in blood flow and nutrition led to persistence and excessive production of trophoblastic cells, to their drawing down into the uterine muscle, and, finally, to their decadence, through a series of retrogressive changes.

It is generally agreed that biologic hormone studies are of very definite value in estimating trophoblastic activity. Since elaboration of the chorionic hormone is a property inherent in the chorionic tissue, demonstrable quantities of hormone are expected to be found in the body fluids of any person harboring such tissue, either normal or abnormal. As far as we know, this expectation has never failed yet, despite the few published reports of misleading results, which threw a justified doubt on the real value of the method. Greenblatt and Pund¹² have mentioned the case of Sehumann and Voegemin in which the histologic diagnosis was inconclusive after two curettings and, because of two negative Freidman tests, operation was delayed. Four months later the patient had a massive hemorrhage; the Freidman test was at this time strongly positive and a hysterectomy was performed. On histologic examination, a typical chorionepithelioma was found, and the patient died five months later of cerebral metastasis. If our understanding of the histobiology of these tumors is correct, no explanation can be offered to justify the early negative chorionic gonadotropin assay (in this case) except possibly unfitted animals or errors in specimens or technique.

Against the conclusive value of the method, Brindeau¹⁶ has stressed the point that because of the prolonged period of hormone elimination, the persistence of a positive assay, after expulsion of the mole, does not necessarily indicate that a malignant change has occurred in the molar rests. This statement was based on Zondek's¹⁷ demonstration that the pregnancy test may remain positive from four to twelve weeks after elimination of the mole. Under these circumstances, if qualitative positive tests may be viewed with suspicion, spaced hormone titration of the blood serum has been shown to permit differentiation between persistence of physiological condition and development of a pathological one. As Payne¹⁸ has pointed out in the discussion of Hertig and Sheldon's paper "the only hormonologic identification of chorionic malignancy rests, not upon a single quantitative or qualitative determination, but upon the demonstration of increased values by means of repeated assays."

One might conclude that an effective distinction between the malignant trophoblastic cell growths, which require radical treatment, and the harmless trophoblastic cell proliferation for which such treatment would represent an undesirable mutilation must be based in each case upon careful consideration of the clinical, pathologic, and hormonal data.

Summary and Conclusions

Disorderly, atypical, overactive trophoblastic cell proliferation and myometrial invasion by large bizarre-shaped cells which showed a marked tendency to fuse together in plasmodial-like formations were the main histologic patterns found at examination of deep uterine scrapings in two cases following miscarriage. In one case, that of a 22-year-old white woman, pregnancy had advanced up to the second month; in the other, that of a 19-year-old white woman,

pregnancy had advanced up to the fourth month. Following the study of the microscopie slides, the impression received was of a so-called syncytioma in the first case and of syncytial endometritis in the other case. Radical treatment was considered in both, but delayed in view of the youth of the patients and of some doubt as to the real malignancy of the condition. The process was followed through frequent gonadotropic hormone tests and repeated curetting. The hormone tests were consistently negative in both cases. In the first case, a curettage after a month revealed a perfectly normal endometrium in the secretory stage of the menstrual cycle. There were no detectable trophoblastic cells in the fragments of myometrial tissue.

In the light of the unusual course of events in these two cases, and in similar cases reported in the literature, it is apparent that the usual criteria of malignancy, which apply so well to the cellular growths elsewhere in the body, cannot be applied strictly to the growths by trophoblastic cells, since free cellular growth, invasiveness, and obliteration of neighboring structures are qualities of the trophoblast under normal conditions.

In the differential diagnosis between benign trophoblastic cell proliferation and chorionepithelioma, it is felt that valid information can be obtained from the intimate structure of the cell type mainly involved in the proliferative process. On the basis of cytologic criteria, namely, absence of mitotic figures, evidence of impending cell dissolution (nuclear hyperchromatism, karyorrhexis, karyolysis) and predominance of "plasmodial patterns" which more and more are considered to represent a form of reduced vitality of the trophoblast, in spite of the cellular atypism and of the deep invasion of trophoblastic cells in the uterine musculature, we decided to treat our cases expectantly. The final outcome proved our judgment to be correct.

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EARLY RISING AFTER DELIVERY*

EDWARD L. CORNELL, M.D., F.A.C.S., AND JOSEPH J. MULLEN, M.D.
CHICAGO, ILL.

(From the Department of Obstetrics, Henrotin Hospital)

EARLY ambulation in the puerperium is taking on increasing interest to the obstetrician and later it will probably occupy attention of the gynecologist.

During the recent war the shifting population made some centers so crowded that hospital facilities could not keep up with the demand. Therefore, physicians and administrators were forced to attempt to admit more patients per bed than was customary. They could do so only by allowing surgical and obstetric patients up earlier, thus hoping to discharge them sooner. Lack of hospital personnel also entered into the problem.

In Chicago after the war, the demand for obstetric care has risen about 100 per cent or more, yet we have no more obstetric beds and bassinets available. Most women do not wish to have their babies at home. The hospitals and the medical staffs have been forced, by demand and by lack of personnel, to shorten the stay of obstetric patients wherever possible.

In Chicago, patients are permitted to stay in the hospital from three days to seven or eight days. The 3-day patients are usually sent home in an ambulance, while those staying five or more days are permitted to leave by private car or taxicab.

Approximately a decade ago, the first attempts at early ambulation following major surgical procedures were instituted. Although varying interpretations have been placed on the results, the procedure seems to be basically sound.

The question of when to allow the patient to get out of bed, for how long a period, and exactly how much freedom of movement is permitted is a point for the physician managing the case to decide.

About eighteen months ago, the Henrotin Hospital was faced with the problem of delivering and housing twice as many patients, with short personnel. The obstetric staff decided it was better to offer at least delivery service and fewer days in the hospital. Previous to this time, the hospital followed the usual generally accepted routine in this community. The patient was allowed to sit up in bed on day 4, to dangle the legs on day 7, up in a chair on day 8, to walk on day 9, and to go home on day 10 to 12.

It was decided to attempt to get all patients on their feet on the fourth day with the exception of those who might have developed complications. For the purpose of clarification, the postpartum day is defined in relation to 6:00 P.M. Those mothers who are delivered prior to 6:00 P.M. commence their second postpartum day at midnight of the same day. Those delivering between 6:00 P.M. and 12:00 midnight commence their first postpartum day at midnight.

*Presented before the Chicago Gynecological Society, March 21, 1947.

On the morning of the fourth day the patient is given an enema and is then encouraged to use the toilet unaided, but accompanied by the nurse. From the toilet the patient returns to a bedside chair where she is allowed to remain for fifteen to thirty minutes, or until the bed linen is changed. The patient is allowed up to the toilet whenever necessary during that day and also to remain seated for fifteen to twenty-minute periods immediately thereafter. The same procedure is followed on the fifth day with the addition of some walking about the room. From the fourth day on, the patient is encouraged to perform as much of her daily ablutions as possible. A basin of warm water, soap, washcloth, and towels are brought to each bedside table.

On the sixth day the patient is allowed to walk around the corridors and to the nursery. On the seventh day she takes a shower and is given complete freedom of action and movement. This continues as long as she remains in the hospital.

The average hospital stay at present is seven days; the number of hospital days is directly related to the number of nursing personnel available.

In following this routine one can expect to meet with objection on the part of some of the patients. Those who have just been delivered of their second, third, or fourth child will many times express amazement at the procedure and in some cases they will be antagonistic. There are various methods to cope with this situation. When the patient refuses to get up at the nurse's bidding, the intern or resident is called to add his encouragement. In the event that this meets with failure, the attending physician is appraised of the facts prior to making his daily rounds. Many times the answer is only to allow the patient another day in bed, and in approximately 5 per cent of this series two extra days were allowed.

Reasons for objecting to arising on a given day are many and varied. The patient who assumes an air of martyrdom will always be present. She has passed through the tortures of labor and is not ready to reveal an uneventful postpartum period by being out of bed.

The observations upon which this present study is made are based on 1,000 deliveries at Henrotin Hospital, representing a typical cross section of postpartum cases. Included in the group are 53 low cervical cesarean sections. Of these, twenty-eight were up to the toilet and sitting in a chair on the first postoperative day, seven on day 2, one on day 3, three on day 4, seven on day 5, seven on day 6. The first postoperative day is defined as the day following surgery.

Of those patients delivered vaginally who were up on day three and four, the following observations have been made:

The first day that the patient is up we recognize an attitude of scepticism or possibly an air of anticipation. She asks herself, "Just how am I going to get along today? What is going to happen?" The patient moves with an air of hesitancy and with varying degrees of discomfort, for many have had an episiotomy. There is a tendency to return to bed in a very short time.

On the second day up the patient has much more assurance of her ability to ambulate. She moves about with freedom of effort. There is an air of confidence reflected in her movement and, in a large percentage of patients, an attitude of a job well done. There are others, however, with a normal degree of emotional stability who retain some doubt as to the advisability of being out of bed. Their remarks are in the nature of the statement that "everything inside me feels as though it is falling out." This thought is expressed equally by the primipara as well as the multipara.

On the sixth postpartum day the patient is effortlessly walking about her ward or room and the corridors. She is inclined to make frequent trips to the nursery to view through the windows her own and other infants. The opportu-

TABLE I. DAY UP

	1	2	3	4	5	6	
Primiparas	3	120	221	52	16	412	
Cesarean section	4	0	2	4	6	28	
Multiparas	1	2	135	287	76	535	
Cesarean section	16	3	0	1	1	25	
Total						1,000	
Per cent	2.9	1.2	25.5	51.1	13.6	5.7	100

TABLE II. DAY HOME

	5	6	7	8	9	10	11	12	13	14	15	16	17	
Primiparas	13	61	90	112	70	41	13	8	1	1	1	1	1	412
Cesarean section		1	5	8	6	6	4	2	1	1				28
Multiparas	20	74	102	148	96	76	9	8			0		2	535
Cesarean section			6	6	6	8	5							25
Total									1					1,000
Per cent	3.3	13.5	19.3	27.1	18.0	13.1	3.1	1.8	.02	.02	.01	.03		100

TABLE III. TYPE OF DELIVERY

	PRIMIPARA	MULTIPARA
Cephalic forceps	352	300
spont.	39	223
Breech forceps	9	2
spont.	12	16
Low cervical cesarean section	28	25
Version & extraction	0	1
Episiotomy	376	370
Total Babies	1007	

ity to observe her child is a source of pleasure to the new mother. From this point on to the time of discharge the routine is unchanged.

At the time of discharge the patient walks confidently and effortlessly out of the hospital. It would be difficult from ordinary observation to classify the individual as a recent parturient. During the period of hospitalization the patient is given the same close observation that has been the rule in the past. With any evidence of complications she is returned to bed rest or to limited movement.

No attempt has been made to run a control group against this series as it is felt that the reaction of the average patient during the customary postpartum period has been definitely established.

TABLE IV. COMPLICATIONS

	PRIMIPARA	MULTIPARA
Episiotomy	Partial separation Up day 4 Home day 12 2nd repair Up day 3 Home day 16	Partial separation Up day 4 Home day 10 Partial separation Up day 4 Home day 11 2nd repair Up day 4 Home day 17
Mastitis	Up day 3 Home day 9 4 11 4 12 5 12 5 14 6 9	None
Urinary tract infection	Up day 4 Home day 9 4 10 4 11	Up day 4 Home day 11 5 9
Mild upper respiratory infection	Up day 4 Home day 8 4 9 5 10 5 10	Up day 3 Home day 6 4 9
Fever unknown origin	Up day 3 Home day 11 3 17	Up day 4 Home day 9
Endometritis	None	Up day 5 Home day 17
Vertigo and syncope	None	Up day 6 Home day 10 4 8
Hemorrhage	None	Mod. severe Up day 5 Home day 12 Mod. severe Up day 5 Home day 10

In this series there were five patients who suffered various degrees of wound breakdown in the episiotomy. Two were considered extensive enough to require a return to surgery. In each case figure-of-eight silk-worm-gut sutures were used for the secondary repair. The remaining three were allowed to heal by granulation. In each case there was some elevation of temperature, with two patients reaching 100.4° F. on two or more days.

Vertigo is not an infrequent symptom but rarely occurs after the first day up. This complaint was not unusual in many who remained in bed under the previous routine of eight or more days.

Vertigo was followed in two cases by syncope. In the first case no explanation could be found. In the second, there was a strong psychic factor which probably contributed largely to this episode. The patient was returned to bed and she was up again on the fifth day without incident.

In none of this series was there detected a case of thrombophlebitis while in the hospital. One patient, a low cervical cesarean section case, who was up on day 7 and discharged on day 12, returned to the hospital with severe thrombophlebitis, eighteen days following discharge from the hospital.

The incidence of proved cystitis was at a minimum, three cases being established by clinical and laboratory methods. *E. coli* was the predominant organism found on culture of the urine.

Mastitis of varying severity from mild to severe was present but it is not probable that this could justly be attributed to earlier rising.

Fever of unknown origin is a factor that will persist. This classification is given only to those patients in whom a thorough study of all genital and extra-genital sources reveals no apparent reason for an elevation in temperature over 100.4° F. for one or more days. The patient returns to bed and remains until the temperature remains normal for twenty-four hours.

It is felt that normal bowel habits are more quickly reestablished with early ambulation. The necessity of catheterization is also reduced. The uterus returns to normal size more rapidly.

There are frequent occasions when it has been found necessary to discharge the patient on day 6 and many times on day 5. The procedure is unchanged irrespective of the day of discharge. The patient in every case left the hospital ambulatory, although we do not attempt to condone or to establish early discharge as a practice, but do this only because of overcrowding. Prior to discharge the patient is instructed to follow a restricted routine at home, one that would correspond to her movement if she remained in the hospital for ten or twelve days.

All the staff at Henrotin Hospital state they find no greater pathology at the postnatal examination than they did when the patients remained in bed eight days or so.

Whether or not early rising will have late aftereffects such as relaxed abdominal muscles, relaxed pelvic floor, prolapse of the uterus, bladder, and rectum remains for the future to determine. Most obstetricians have felt that bed rest of a week or more was necessary for the proper return of the pelvic organs to normal. Thirty years ago it was customary to keep patients in bed twelve to fourteen days. Most women then did not fully return to their predelivery state under six weeks. With earlier rising, most women today feel as well as they did before delivery in about fourteen days. Perhaps this is better, but who knows? Will our American women be as good looking at 45 years, or will they look old at 35, like the Indian women in Central and South America where they resume their usual routine in twenty-four to forty-eight hours?

Conclusions

One thousand patients were allowed up on day 6 or earlier with 80 per cent of these being up prior to day 5. These patients are apparently in much better condition at the time of discharge than if they had remained in bed for eight or more days. They are in a position to adapt themselves more readily to their daily household routine. Episiotomy wound healing was not adversely affected nor was morbidity increased.

No case of thrombophlebitis occurred in those delivered vaginally, which causes us to believe the tendency toward this complication is reduced.

No case of uterine prolapse occurred. The rate of involution of the uterus is increased.

When necessary, because of overcrowding, the patient may be discharged from the hospital earlier than heretofore with a greater margin of safety.

The postoperative course of the cesarean section cases is more nearly uneventful. Distention is infrequent. The necessity for catheterization and enemas is lessened when the patient is up to the toilet on postoperative day one. One case of thrombophlebitis occurred thirty days post operation.

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Discussion

DR. ALFRED J. KOBAK.—The wide range of possibilities as reported in this paper does not indicate to what extent the authors themselves allow their own patients out of bed following vaginal deliveries and following cesarean section. Emil Ries was probably the father of early ambulation; about forty-eight years ago he wrote a paper which appeared in the *Journal of the American Medical Association* on this subject. His colleagues were reluctant to accept his views. He was far ahead of his period and consequently his suggestions were ignored. From time to time afterward, there appeared contributions by general surgeons which indicated the possibility of early ambulation. In the past twenty years there has been a recognition of early ambulation, and latterly patients delivered vaginally have been given attention in this same respect by permitting them out of bed early. Recently a volume appeared by a surgeon in which the physiologic principles of early ambulation were discussed. The author contends that there are fewer pulmonary and circulatory complications with consequent thrombosis and emboli, less abdominal distention, and less wound complication.

In the literature we find reports of animal experimentation in which dogs and rats were subjected to early ambulation and in the control animals early ambulation was avoided. It was found that the animals that rose early had far better recovery.

We began our studies on obstetric early ambulation in the early part of 1940 at the Cook County Hospital. We were inspired by the reports in the magazines of the air blitz over London where patients were removed from their beds. We had no known principles to guide us, but we let the patients up on the fifth, then the fourth, third, and second days. We studied 500 such cases and we were entirely satisfied that these patients had better results in convalescence when compared with the control group. We were prompted to try another 500 but because of the shortage of nurses the study was not completed. We recently resumed this study. In Ward 51 of the Cook County Hospital we house patients who have a normal uneventful pregnancy and these patients we ambulated on the second day. There were 1,417 with a corrected morbidity of 1.7 per cent. In the control cases that were up on the fifth and sixth days there were 847 and the morbidity was 2.8 per cent.

A study of three months' duration was conducted on patients in Ward 50 which houses those with septic complications. These were allowed up on the sixth day. There were 123 with a morbidity of 2.66 per cent and 84 with a morbidity of 4.55 per cent. These patients had a morbidity 1.7 times higher than the early-ambulated cases.

Concerning cesarean section, for three months we had 33 cases permitted out of bed as compared with a control group of similar size. The average postoperative stay was nine days as compared to 13 days in the control group. The morbidity incidence was 6 per cent as compared to 10 per cent. There were more inhalation anesthetics in the control group and more spinal and local in the group studied.

In asking the nurses concerning the progress of the people ambulated early, they reported it was entirely satisfactory but they did observe that the lochia was more profuse on the first day, but the day after it decreased. Involution occurred rapidly. There was less necessity for use of the bedpan; most patients would prefer to go to the toilet and eliminate the uncomfortable posture of using a pan in bed.

I feel the authors did not get full benefits of early ambulation, that their ambulation was resorted to rather late. We have ambulated our patients much earlier. It was shown in the book referred to that cases that were ambulated soon after anesthesia, on the first and second day, did much better. He quotes the work of de Takats and others showing that trauma at the time of surgery gives rise to changes in the blood that cause the blood to coagulate more rapidly. This together with the fact that the patient is immobilized are factors which lead to thrombosis. If thrombosis can be prevented it has to be prevented by early ambulation.

DR. GARWOOD C. RICHARDSON.—The authors have recommended early ambulation apparently as a relief for the crowded situation in many of our hospitals in Chicago and throughout the country. Those of us who practice early ambulation at Wesley Hospital do so for the virtues of the procedure itself; in other words, for the benefits we feel the patients derive from early ambulation. During my internship days at the Ancon Hospital in the Canal Zone, in 1921-1922, patients were gotten out of bed on the first postoperative day after major surgery. Certainly the literature cites many articles in surgery and in obstetrics where early ambulation has been practiced. In their opening statement the authors say that it will probably be extended to gynecology. By certain doctors early ambulation in gynecology has been practiced in Wesley Hospital as long as early ambulation has been practiced in obstetrics.

According to the authors, the sixth day is apparently the accepted criteria for early ambulation. We feel that early ambulation should not be extended over a three-day period. If you really are practicing early ambulation for the sake of early ambulation, the patient should be gotten up on the first or second day and certainly by the third day. At Wesley Hospital since early ambulation was instituted we have had 4,101 deliveries. Our attending men there are divided into three groups: Those of us who get our patients up from the first to the third day compose the first group, and the number of those cases amounted to 1,247. The second group are probably just a little hesitant—they constitute some of the younger men—and they get their patients out of bed in four or five days. The number there was 174. The third group constitutes those men who get their patients up from the fifth to the sixth day. That is probably due to the policy that we have adopted of not requiring anyone to go home earlier than eight days. The number in this group was 394, making a total within the six-day period of 1,115 cases.

We believe that the patient is definitely benefited by early ambulation. We have tabulated the observations of attending men, nurses, interns, and residents. There are about eleven benefits that we see are derived from early ambulation.

1. Voiding is more spontaneous, with a definite decrease in the number of cases that have to be catheterized.

2. Defecation normally is earlier than usual. We do not use enemas except where necessary in those cases that are allowed up early.

3. The perineal comfort of the patient is definitely benefited. Early ambulation and proper exercise of the muscles in the region of the episiotomy wound cause much more rapid recovery.

4. Fainting has been practically eliminated. Many patients faint when gotten up on the eighth day; practically none faint when they are gotten up on the first to the third day.

5. Involution is aided. That is an observation that even student nurses have noted quite commonly. By the time the patient goes home you can very frequently not feel the uterus abdominally.

6. Total hemorrhage is lessened.

7. The patient is happier, we find, rather than skeptical. That could be due to the fact that we do not just give her a surprise when she is in the hospital by telling her we are going to get her up early, but include that as part of her prenatal care. All my patients are informed during their prenatal care that they are to be gotten out of bed on the first to the third day, depending on their condition. In my own cases I have had only two complaints, and these two individuals refused to get up early.

8. Thrombophlebitis is lessened. Embolism has been cited in the literature as being lessened. In the studies presented this evening the period has not been long enough to bring out the possibility of lessened frequency of embolism.

9. We are reporting less morbidity than formerly.

10. The patients practices self-care earlier in her hospital stay and thus reduces the burden upon the nursing staff.

11. We have had no cases of complete disruption of the episiotomy repair.

In the tabulation of cases as presented by the authors, they show a total of 1,000 cases over a six-day period; 511 of those were gotten up on the fourth day and only 296 were allowed up in the first three days. That is only about 30 per cent that really qualify as what we would consider truly representative of early ambulation. In the portion of the table that was accompanied by complications, there were 55 cases representing 74 patient-days where the stay was beyond ten days, clear up to as long as 16 days in one case and 17 days in another case. It is not clear from the tabulation whether those were early ambulation cases or what the complication was. It does seem that that number of patients and that number of patient-days are a little bit excessive in a report presenting 1,000 cases.

DR. JOHN BREWER.—At St. Luke's Hospital for many years we have been getting our patients up between eighteen and thirty-six hours postoperative. That includes all gynecologic procedure, vaginal and abdominal.

DR. C. O. McCORMICK, Indianapolis, Ind.—At our hospital it has been our impression that we had fewer residual complaints and fewer emboli when we practiced early ambulation.

I would like to ask regarding circumcising the babies. Is it done immediately or are the patients allowed to go home and later return for this procedure?

DR. J. P. GREENHILL.—I would like to emphasize one important aspect of the subject. Those of you who read the Year Book know that I am in favor of early ambulation. I learned it from Emil Ries. His paper in 1899 was the first one in this country on this subject and the next one was by Howard Kelly of Baltimore in 1911.

There is a definite connection between lying in bed and the incidence of thrombosis and embolism, both fatal and nonfatal. Erdheim of Vienna taught his classes that the source of his emboli, both fatal and nonfatal, was in the calf vessels. To try to dissect out every vessel in the calf was an enormous task. He cut clear across the calf and found, to his amazement, that while there was the preparation of a thrombus in the veins there was no evidence of thrombosis. In the last few years a number of investigators in this country and abroad followed up that study, and in one series there were 26 per cent of thrombi and in another series 50 per cent. In one group in which there was a series of fatal emboli, every single death occurred in patients who had been in bed from the time of the operation to death. Not a single embolus was found in patients who had been up shortly after surgery. In these studies, if early ambulation was not possible, then they made the patient move about in bed. I think the older men and some of the younger who are still skeptical should read these papers.

DR. ROBERT M. GRIER.—At Evanston Hospital we get our patients up early. As to morbidity with special reference to breast abscess, I think the morbidity would be greatly lessened if we sent the patients home on the first day.

DR. W. J. DIECKMANN.—For over fifty years there have been enthusiastic reports every ten to fifteen years about early ambulation. The reports are always favorable but soon most hospitals discontinue early ambulation without reporting the reason. If it is so wonderful, why has it been given up in the past? I do not like the term "getting on the band wagon," concerning early ambulation for obstetric patients. I do not know if it is good or bad for the patient. As the result of studies on puerperal infection in 1925, I have always believed in early activity of the patient in bed. Whether or not she has to be up is still debatable. I am certainly opposed to the discharge on the third, fifth, or seventh day post partum. I do not believe any hospital is justified in this procedure. When beds became scarce, the hospital authorities and city authorities should have cooperated and made beds

available. Much of the elective surgery, gynecologic and general, could have been omitted during the emergency. I do not believe the doctor should have assumed the responsibility for taking care of the increased obstetric load by merely discharging patients at earlier dates.

When one considers early ambulation, there are several questions; (1) Is it good for the patient in that complications are decreased, and are her general morale and strength better two weeks after delivery than they would be were she kept in bed the usual length of time? (2) Does it decrease the amount of nursing care and thereby reduce hospital costs? I am quite certain that there will be a scarcity of nurses for a long time and, if nurses are paid what they deserve, hospital costs will increase instead of decrease. They are already very high for the family with the average income. If the costs of hospital care can be decreased without endangering the patient, it is worth while.

I am opposed to patients being discharged before the tenth day, which I think is too early, and would prefer the fourteenth day, the reason being that once the mother is home she is concerned with the general management of the house, irrespective of how many servants there may be. There is less or no control of visitors possible. There are disadvantages in the hospital, but I believe that those at home outweigh those in the hospital.

For economic reasons we began over twelve years ago to have our obstetric patients bathe themselves on the second postpartum day. This has continued to date and we have believed for some years that this early activity in bed is of value. The sick patients, of course, have complete nursing care. On October 1, we began letting a limited number of patients up earlier in the puerperium. The doctors and nurses were pleased with this trial period. Since January 1, all obstetric patients including cesarean section cases are out of bed in a chair twenty-four hours after delivery, and forty-eight hours after delivery are permitted in the bathroom which adjoins their bedroom and by the sixth day after delivery are permitted in the corridors of the hospital. The only patients who do not get up are patients from whom it is necessary to obtain the urine by a retention catheter, for instance, toxemic patients, or patients who have had major complications. All the doctors on the staff are co-operating in this endeavor. To date there have been no increased number of complications and the nursing staff states that the amount of nursing care has been decreased tremendously. No patient is compelled to get up, and patients are discharged on the tenth day, or, if the bed is not necessary, are permitted to stay longer.

We expect to compare our statistics at end of this year with those of preceding years and from a comparison of that data decide whether or not we will continue early ambulation.

Early ambulation in our hospital was not instituted to enable us to increase the number of deliveries or to facilitate the early discharge of patients. We insist upon patients staying the prescribed number of days, which is a minimum of ten.

DR. FREDERICK H. FALLS.—We heard it stated here that Emil Ries said it was a good thing to take patients out of bed. If you had talked to John B. Murphy he would have said it was not a good thing. E. Wyllys Andrews would have said it was not a good thing. If you asked Graves at Harvard he would have said, you had better keep a perineorrhaphy case in bed for sixteen or seventeen days and you will get better results. This idea of getting all excited about a situation that is present with us at this time is ill advised. It has been precipitated by this war condition and somewhat by spinal anesthesia. The reason for this wave of spinal anesthesia was because the Army and Navy did not have anesthetists and they could not get them, so they stuck a needle in the back of the patients and operated upon them without a proper type of anesthesia.

If you know anything at all about labor, and especially the second and third stages, and if you ever put your hand in the vagina and felt a flaccid ureterosacral ligament and perineum, it seems to me you will agree that to put the weight of a puerperal uterus on this ligament the first, second or, third day is ill advised if you do not have to do it. It does not make any difference whether these women leave the hospital without fainting, that does not mean anything. Maybe they do feel better and maybe they are stronger on their feet, but that does not tell what is going to happen to those women in ten or fifteen years. The

only way to settle it is to take every other case—and you have to take enough of them, 1,000 or 5,000 to find out and then you will begin to see the difference. I do not believe we will know whether the women who have been allowed to be up are better off than those who were kept in bed longer for another ten or fifteen years. Then we will know whether somebody has done them a favor or an irreparable wrong.

DR. CORNELL (Closing).—Some of the men misread the title. It was "early rising after delivery," not after gynecologic operations. The statement was made that the gynecologist would be interested in these patients at a later date. It had nothing to do with early rising in gynecology.

The second thing is that we have a similar situation to that which Dr. Richardson has at Wesley. Most of our patients are private patients. It is, as you know, rather difficult to get physicians to agree, even in a more or less closed staff. We have some doctors who wish to have their patients up on the third day, some on the sixth, and some on the eighth day. It is only recently that some of the men have come around to earlier rising. That is the reason you see the figures that were mentioned in these 1,000 cases. In the past six months most of the men operating at Henrotin Hospital permit their patients to get up on the third day and they are discharged on the fifth to the seventh day if there are no complications. The ones that were in the hospital sixteen and seventeen days were patients that had secondary repair of episiotomies. Aside from that, there were none of the early rising patients who stayed longer than ten days with the exception of a few who had had cesarean sections.

About six months ago I started to get the patients who had cesarean section up early, I had a considerable amount of difficulty with the patients themselves. It was only by moral persuasion and getting the patient out of bed myself that I was able to get them to sit in a chair the second day. The distention is practically nil, we have fewer catheterizations and the uterus seems to involute better. I am not sure whether it is good policy or not. As you probably all know, I was brought up by Dr. DeLee, who definitely advocated, when I was first with him, twelve days in bed. It took several years before he permitted a patient to get up in ten days and finally in nine days. I do not think he would advocate getting them up on the first, second, or third day. I do not believe I am going to live to see the patients I deliver now come back with gynecologic problems, the result of early ambulation. Whether or not they are going to have relaxed perineums for the gynecologist to repair, prolapses and other things, it is difficult to say. I have a feeling that some of the younger men will see these patients. I just wonder whether it is good policy. I have a feeling that it would be wise for us to go back and keep these patients in bed a little longer and keep them in the hospital a little longer. I have seen Indian women in Central America and Guatemala who get up twenty-four hours after delivery, but these women look old at 30 or 35 years.

In answer to Dr. McCormick's question, the babies return later for circumcision.

It seems to me that the number of cases of mastitis is somewhat lessened, though 1,000 cases do not mean anything. I just want to leave the thought with you that I do not believe we are doing our patients any good by permitting them to get up as early as possible and to allow them to go home as early as possible.

ACUTE PUERPERAL MASTITIS

Clinical and Bacteriologic Studies in Relation to Penicillin Therapy*†

H. CLOSE HESSELTINE, M.D., CHARLES G. FREUNDLICH, M.D., AND
K. EILEEN HYTE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and the Department of Bacteriology and Parasitology, The University of Chicago, and the Chicago Lying-in Hospital)

ACUTE mastitis is a serious medical and psychological complication of the puerperium, especially if suppuration occurs. It is serious medically: first, because it may be extensive and destructive and may endanger life; second, because it may be associated with multiple or chronic recurring abscesses, thus having a deleterious effect upon health; and third, because it interferes with proper lactation and almost always necessitates the discontinuance of breast nursing. Acute mastitis is serious psychologically because it disrupts the home and necessitates hospitalization; because the patient becomes anxious about further complications incidental to her puerperium; and because of fear of a similar experience in any subsequent lactation. Irrespective of the time of the development of mastitis, the patient is not psychologically prepared for this complication.

Among our patients, mastitis has been most often observed within the first eight weeks of the puerperium, usually after the tenth day. However, observations beyond the third month have been limited, due to the small number of mothers continuing breast feeding after this time.

The early treatment of acute mastitis may often bring about subsidence without suppuration. On the other hand, virulence of the infection, lowered host resistance, or delayed treatment may explain unfavorable results. Prior to the use of penicillin, the only effective but seldom employed method for treatment was the immediate drying of the breasts after delivery. Ordinarily such a routine would seem too great a price to pay. The report of Hodgkinson and Nelson¹ on 24 patients with acute puerperal mastitis who were spared suppuration by the use of penicillin seemed to give the impression that suppurative puerperal mastitis could be completely avoided by the use of penicillin therapy. Using the same treatment, Power and Cravotta² obtained cures within forty-eight hours in 25 cases of acute mastitis. Hence, penicillin was acclaimed a panacea for human mastitis.

Somewhat different results observed at the Chicago Lying-in Hospital have stimulated the present report. This study includes observations on 210 patients with suppurative mastitis seen during the last thirteen and one-half

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years. Penicillin therapy of acute mastitis, the local application of penicillin ointment during lactation, some possible sources of the causative *Staphylococcus aureus*, and the resistance of some of the isolated bacteria to penicillin have been studied.

Penicillin Treatment of Acute Mastitis

Twenty-three consecutive patients with acute puerperal mastitis were treated only by the administration of penicillin. Of these patients, eleven were completely cured without any residual damage or lesions in the breast, six had residual or slowly subsiding induration, while the remaining six had localized abscesses, confirmed by incision and drainage. The dosage of penicillin was 20,000 units intramuscularly every three hours (8 times daily), except in three patients (Nos. 4, 5, and 9), who received 15,000 units every three hours. The total dosage of penicillin, number of days of treatment, duration of symptoms prior to therapy, the persistence of fever, and other facts relative to these patients are shown in Table I. On the average, the six patients who developed

TABLE I. RESPONSE OF MASTITIS TO PENICILLIN THERAPY

CASE	AGE	PARA	BREAST	DAY POST PARTUM	PENICILLIN*		SYMP- TOMS (HOURS)	BECAME AFEBRILE (HOURS)	RESULTS
					TOTAL	DAYS			
1	20	i	Left	19	420,000	4	24	18	Good
2	20	i	Bilat.	12	800,000	5	48	48	Good
3	23	i	Right	9	435,000	4	24	36	Good
4	27	i	Right	8	340,000	5	48	24	Good
5	20	ii	Right	16	315,000	3½	12	12	Good
6	29	ii	Left	66	320,000	2	18	12	Good
7	30	ii	Right	8	700,000	5	12	6	Good
8	30	ii	Right	8	750,000	5	12	48	Good
9	33	ii	Left	12	240,000	3	24	24	Good
10	29	iv	Right	29	480,000	3	40	12	Good
11	29	iv	Left	71	750,000	5	24	6	Good
12	18	i	Right	26	960,000	6	9	48	Induration persisted
13	30	i	Right	150	210,000	4	72	24	Tenderness persisted
14	22	ii	Right	15	320,000	2	48	12	Induration persisted
15	23	ii	Right	28	780,000	6	12	12	Subsided slowly
16	32	ii	Left	45	850,000	6	96	36	Subsided slowly
17	24	iii	Right	29	960,000	6	36	48	Induration persisted
18	23	i	Left	14	800,000	5	36	24	Abscess—incised
19	24	i	Right	17	750,000	6	120	48	Abscess—incised
20	24	i	Right	10	230,000	2½	96	48	Abscess—incised
21	25	i	Left	42	530,000	5	144	36	Abscess—incised
22	29	ii	Left	12	640,000	4	24	24	Abscess—incised
23	20	iv	Right	16	640,000	4	96	24	Induration persisted
Readmitted 2 weeks later					480,000	3			Abscess—incised

*20,000 units every three hours, 8 times daily, except cases Nos. 4, 5, and 9, dosage 15,000 units.

suppuration presented themselves late in the course of the disease, a fact which may explain in part the unfavorable results. In these six patients, symptoms had existed from 24 to 144 hours before the institution of penicillin therapy, whereas the longest period preceding treatment in the nonsuppurative cases was forty hours. The white blood cell count before therapy varied from normal to over 25,000 cells per cubic millimeter. All 23 patients became afebrile within forty-eight hours and two patients remained afebrile after six hours of treatment. The fact that patients became and remained afebrile is not proof that the patient has been completely cured, as is shown by the development of abscess in six patients during treatment (Figs. 1 and 2). The white blood cell counts

became normal within a day or so in almost all instances. Although a local abscess remained, these patients felt greatly improved. As will be noted, Patient 23 was readmitted two weeks after the initial hospitalization and after discontinuance of penicillin therapy for drainage of the abscess. Another patient not included in the present group had a localized abscess for sixty days, during

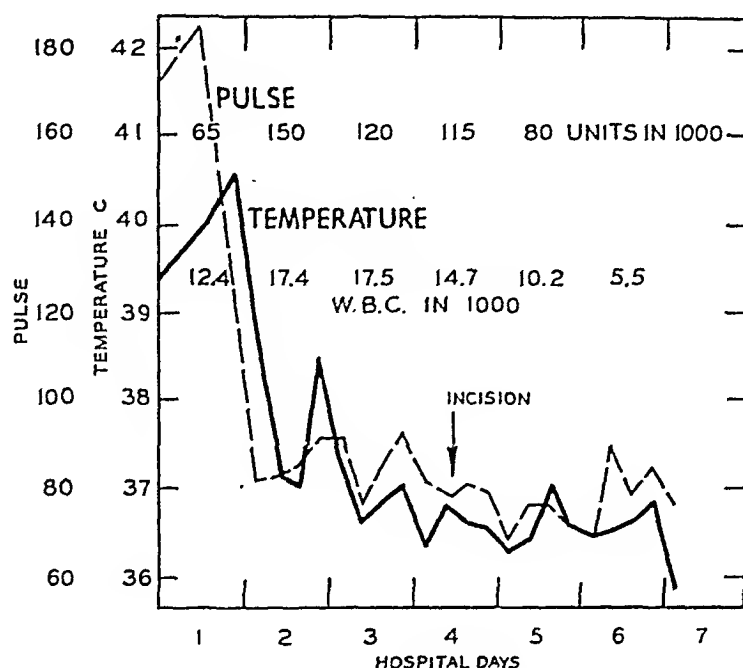


Fig. 1.—Penicillin in acute mastitis, six weeks post partum.

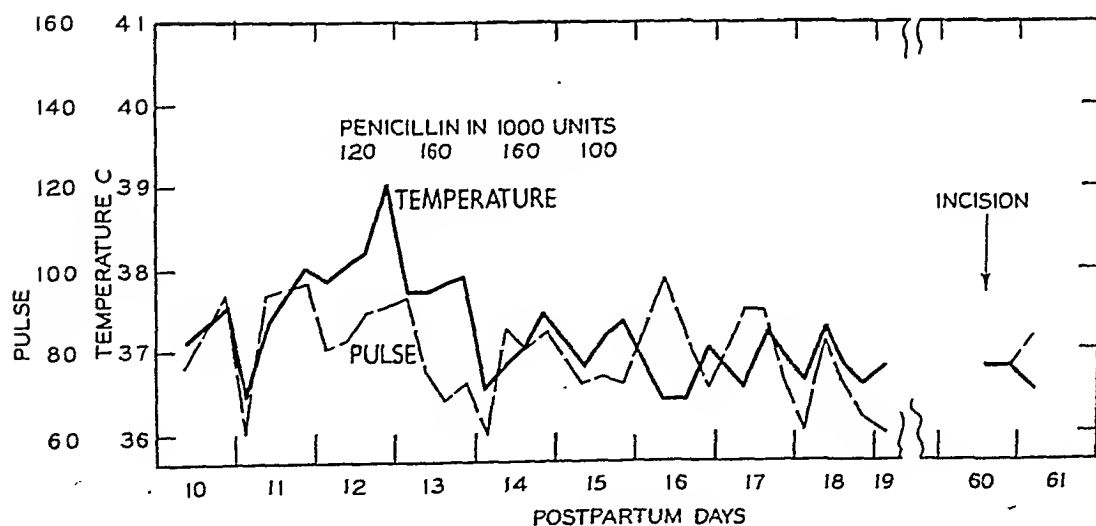


Fig. 2.—Penicillin in acute mastitis.

which time she was afebrile after the second day and maintained a normal white cell count. Cultures from five patients of the present series revealed staphylococci, four of which were hemolytic *Staph. aureus*. The fifth was identified as *Staph. albus*. The culture taken from the sixth patient (No. 19)

was unfortunately lost and a repeat culture was not obtained. It is thus apparent that with persistence of a gross lesion the patient must not be considered cured, and that in five of these six patients the staphylococci were able to survive in the local lesion during antibiotic therapy and to stimulate sup-
puration.

As will be remembered, it was necessary to use the sulfonamides within the first twelve to twenty-four hours in acute puerperal mastitis, if suppuration was to be avoided, and when it occurred during this therapy, suppuration was delayed for several days. Unlike the sulfonamides, penicillin did not increase the time required for abscess formation.

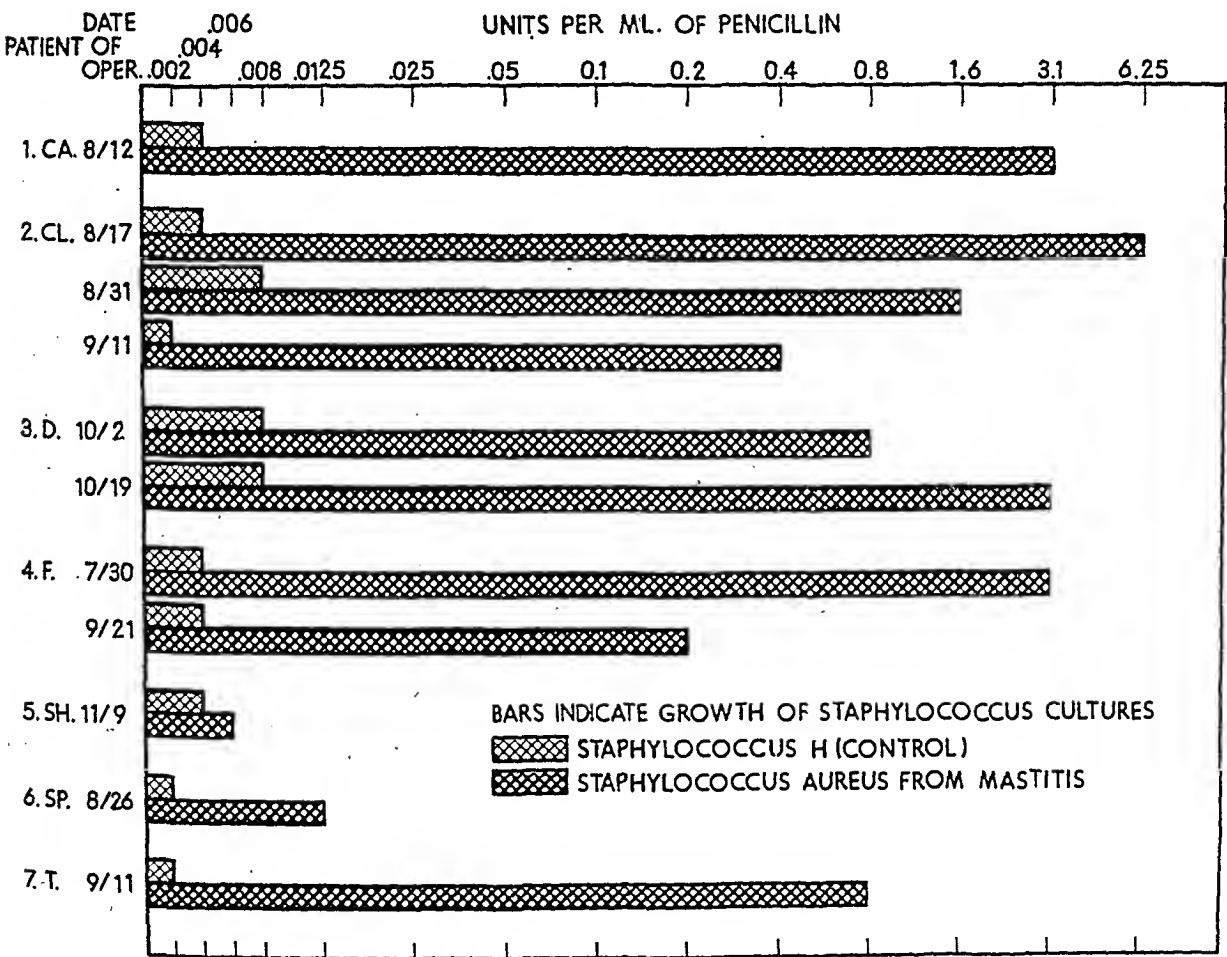


Fig. 3.—Resistance to penicillin of strains of *Staphylococcus aureus* from suppurative puerperal mastitis.

Penicillin Resistance of Staphylococcal Strains

The above observations suggested the desirability of studying the penicillin resistance of staphylococci isolated from breast abscesses. Consequently, staphylococci isolated from eleven abscesses occurring in seven patients were tested for penicillin resistance by the tube dilution method (Kolmer³) soon after their isolation. All of these cultures were hemolytic and coagulase-positive *Staph. aureus*. The results of these titrations are shown in Fig. 3. It will be observed that the resistance of these strains varied from 0.006 to 6.25 units per cubic centimeter of penicillin; seven cultures resisted a concentration of at least 0.8 units and four grew in 3.1 or more units of penicillin. The latter tolerances

exceed the anticipated levels of penicillin in the blood of patients treated by the usual dosages of antibiotic (Rammelkamp and Keefer⁴). In similar titrations the standard Oxford strain H of *Staph. aureus* resisted from 0.002 to 0.008 unit per cubic centimeter of penicillin. The observations do not indicate whether these staphylococcus strains were originally resistant to penicillin or whether resistance was acquired during antibiotic therapy. Furthermore, the barrier action of inflammatory tissue to passage of penicillin has not been investigated.

TABLE II. INCIDENCE OF WOMEN HAVING ONE OR MORE BREAST ABSCESES IN COMPARISON TO THE NUMBER OF WOMEN DELIVERED ON A YEARLY BASIS AND THE AVERAGE FOR THE 13½ YEARS

YEAR	MOTHERS	ABSCESES (TOTAL NO.)	PATIENTS HAVING ABSCESES (NO.)	PATIENTS HAVING ABSCESES (PER CENT)
1933-34	2,621	42	29	1.1
1934-35	2,909	29	24	0.82
1935-36	2,394	29	22	0.91
1936-37	2,341	10	7	0.29
1937-38	2,815	17	15	0.53
1938-39	2,718	31	18	0.66
1939-40	2,593	9	9	0.34
1940-41	2,827	11	10	0.35
1941-42	3,204	11	10	0.31
1942-43	3,766	17	13	0.34
1943-44	3,548	21	17	0.47
1944-45	3,431	16	13	0.37
1945-46	3,493	14	12	0.34
1946 (6 mo.)	1,969	15	11	0.55
Totals	40,629	272	210	0.51

TABLE III. NUMBER OF BREAST ABSCESES BY MONTH FROM JULY, 1933, THROUGH JUNE, 1946, AND FROM JULY THROUGH DECEMBER, 1946, TO EVALUATE SPECIAL TREATMENT*

	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.	FEB.	MARCH	APRIL	MAY	JUNE	TOTAL
July, 1933, to June, 1946	26	16	15	10	16	24	21	13	18	12	16	12	
July-December, 1946	2	3	2	2	1	1							
13½ yr. quar- terly totals		64			54			52†			40†		210
Average num- ber per month		1.52			1.28			1.33			1.02		1.31

*Monthly averages are taken from quarterly totals.

†Only 39 months included in these entries.

The Prophylactic Use of Penicillin Ointment

A study has been made of the effect of the local application of penicillin ointment on the incidence of suppurative mastitis in nursing mothers. As a basis for comparison, a review has been made of suppurative mastitis in patients at the Chicago Lying-in Hospital from July 1, 1933, through Dec. 31, 1946 (Table II). The data include the number and percentage of patients developing abscess during each fiscal year. No account is made of the small, probably insignificant, percentage of patients who did not nurse their babies. It will be noted that the highest incidence of suppurative mastitis (1.0 per cent) occurred in 1933-1934, and that the lowest incidence (0.29 per cent) occurred in 1936-1937. During the entire 13½ year period, a total of 210 in 40,629 delivered

patients developed breast abscess, an incidence of 0.51 per cent. The total number of abscesses was 272. The incidence within the last six months (0.55 per cent) of the period under study was slightly higher than the average for the period (0.51 per cent) and higher than that encountered during the preceding two years (0.34 and 0.37 per cent yearly). In Table III the data are arranged by months. Of the 210 patients, 104 were seen between April and September and 106 between October and March. The lowest number per quarter-year occurred in April through June and the highest in July through September. The monthly incidence rates have not been calculated. The expected number of abscesses per month varied from about 1.0 to 1.5, the mean (arithmetic average) for the total period being 1.31 abscesses per month.

From July 1 through Dec. 31, 1946, the study of the prophylactic use of penicillin ointment was conducted. Only those patients who were lactating were included in the program. For this study the patients occupying rooms in the main building were divided into two groups (Table IV). Between July 1 and September 30, every nursing mother in both groups applied penicillin ointment to the nipples immediately after nursing. The ointment was a commercial preparation containing 1,000 units of the antibiotic per gram of oil base. The antibiotic potency was found to be maintained for at least ten days at room temperature during summer weather (August). The patients received approximately 2 Gm. of ointment (2,000 units of penicillin) at each treatment. Applications of ointment were started as soon as nursing was begun and were continued throughout the hospital stay and after the patient was discharged. The ointment was thus probably used for a total period of six to eight weeks, although application of ointment could be supervised only during the ten-day period of hospitalization. The rationale of the treatment was that local penicillin might prevent invasion and multiplication of staphylococci through the lacteal ducts. During the period, a total of 53 nonsuppurative and 18 suppurative cases of mastitis were observed in a total of 865 lactating mothers, an incidence of 6.1 and 2.0 per cent, respectively. The incidence rate of breast abscess was definitely higher than the average observed previously. It should be noted, however, that, in this study group, calculations of rates are based on the number of lactating mothers and not on total deliveries. From October through December, penicillin ointment was continued in Group I but was omitted in Group II, the only local care in the latter group being daily soap and water cleansing in the morning, and wiping with a clean dry cloth after nursing. The incidence of mastitis was essentially the same in the two groups. It is thus evident that the local use of penicillin ointment did not prevent the development of mastitis or of suppuration. The October-December study does not support the view that the use of ointment increased the incidence of mastitis.

TABLE IV. EFFECT OF PENICILLIN OINTMENT ON THE INCIDENCE OF NONSUPPURATIVE AND SUPPURATIVE MASTITIS IN LACTATING MOTHERS FROM JULY THROUGH DECEMBER, 1946

	LACTATING MOTHERS	NONSUPPURATIVE		SUPPURATIVE	
		NO.	PER CENT	NO.	PER CENT
<i>Treated</i>					
July-Sept.	865	53	6.1	18	2.0
Groups I and II					
Oct.-Dec.	477	41	8.6	7	1.5
Group I					
<i>Untreated</i>					
Oct.-Dec.	388	27	6.9	5	1.3
Group II					

staphylococci in the nasopharynx within the first ten days of life. It is interesting that staphylococci were found in 20 of the 30 mothers, but less frequently in the series of cultures. By inference it seems likely that the nursing baby is a source of infection in puerperal mastitis. Final proof of this hypothesis is hindered by the difficulty of identification of staphylococcus strains. Other possible sources of infection include the skin and the lower genital and intestinal tracts of the patients or contacts.

The penicillin resistance of 60 nasopharyngeal strains of staphylococci was determined (Fig. 4). These cultures were from 29 mothers and 31 babies. It is evident that 7 of the 31 strains from babies were resistant to 0.5 or more units per cubic centimeter of penicillin, as were 3 of the 29 strains from the mothers.

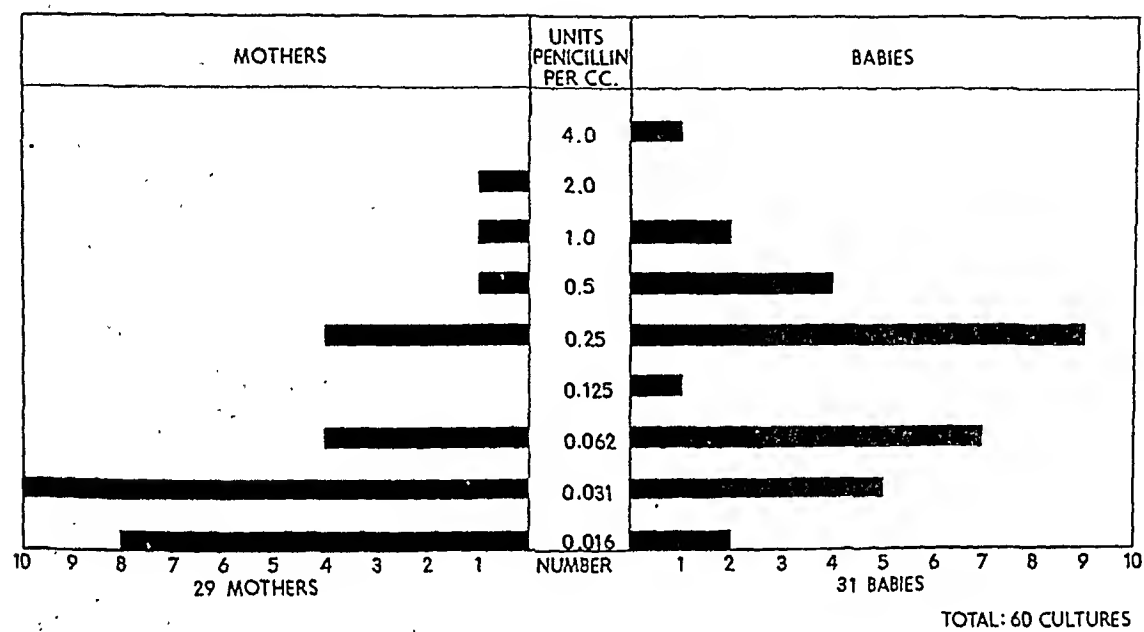


Fig. 4.—The degree of resistance to penicillin by the *Staphylococcus aureus* isolated from the nasopharynx of mothers and their babies after the second and before the tenth postpartum day.

Discussion

The present work indicates that infection of the breast may occur in lactating mothers from the patient herself or from the nursing infant. Contributing factors, such as trauma to the nipple or breast tissue, which we believe to favor the development of mastitis, have not been evaluated in the present study. Although our results suggest the importance of the nasopharynx, other possible sources of infection must, of course, be recognized, and these have not been eliminated in the present series of patients.

The staphylococci cultures isolated from breast abscesses and from nasopharyngeal cultures of mothers and infants varied considerably in susceptibility to penicillin, but some strains from all sources had a significantly high resistance to the antibiotic. This resistance would appear to be a factor in the development of suppuration during penicillin treatment of some patients having mastitis, and should be considered in the determination of "adequate" penicillin therapy.

Thus, Rammelkamp and Kirby⁵ found that 25,000 units of penicillin given intramuscularly every two hours would produce optimum continuous levels in the blood for staphylococcus infection. They further state that the continuous intravenous infusion method, using 100,000 units per twenty-four hours should produce a level of 0.1 units per cubic centimeter, and 400,000 units would yield an average level of about 0.4 units per cubic centimeter, whereas subcutaneous administration resulted in only one-half as great a level. The observations by Goerner, Geiger, and Blake⁶ compare reasonably well. By contrast, Gerber, Schwartzman, and Baehr⁷ found a peak of 6 units per cubic centimeter following 100,000 units given intramuscularly. Accordingly, a peak blood concentration of 2 units would require not less than 33,000 units and probably more than 50,000 units every three hours. From their data, it would appear that sustained blood levels of 2 units per cubic centimeter would not be obtained by the customary dosages, and that the usual penicillin blood levels would be sufficient only if the causative microorganism is particularly susceptible.

Progression of the disease process to suppuration and the necessity for incision and drainage in a number of patients in our series indicate the inability of penicillin treatment to arrest the infection in some instances. Late treatment, the resistance of some staphylococcal strains to penicillin, and the localizing effect of the inflammatory tissue would seem to contribute to this reaction. Increased dosage of penicillin seems desirable for infections with organisms of higher than usual resistance to the antibiotic. The use of penicillin ointment locally on the nipple after nursing was in this study an unsatisfactory prophylactic measure against puerperal mastitis.

It should perhaps be emphasized that puerperal mastitis is a serious medical complication of the puerperium. It is also psychologically disturbing to the patient and may create a complex problem when these mothers must be readmitted to the hospital for treatment.

Conclusions

A report is made of observations of a total of 210 patients having suppurative puerperal mastitis. Suppuration was observed in 6 of 23 consecutive mastitis patients receiving penicillin therapy.

Eleven strains of staphylococci isolated from suppurative mastitis grew in the presence of from 0.006 to 6.25 units per cubic centimeter of penicillin. A significant proportion of these strains were resistant to the antibiotic, since four grew in at least 3.1 units per cubic centimeter.

The local use of ointment containing penicillin after nursing failed to affect the incidence of mastitis in postpartum patients. The incidence of mastitis in lactating patients receiving local treatment with penicillin is compared with that in a control group over a three-month period and with an uncorrected incidence of suppurative mastitis in the Chicago Lying-in Hospital during the past thirteen years.

Nasopharyngeal cultures from mothers and babies were examined for *Staphylococcus aureus*. Twenty-one of 30 babies were found to harbor *Staph.*

aureus during the first ten days of life, as were 20 of the 30 mothers. Ten of these staphylococcal strains were resistant to 0.5 or more units per cubic centimeter of penicillin in vitro. The significance of these findings to the source of infection in puerperal mastitis is discussed.

We thank Schenley Laboratories, Inc., for generously supplying all of the penicillin ointment for that part of the study.

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Discussion

DR. FREDERICK H. FALLS.—It becomes necessary to evaluate the use of penicillin in the various infections that arise in pregnant women. It is important that Dr. Hesseltine has made a careful study of penicillin as far as puerperal mastitis is concerned. I agree with him as far as our experience has gone, but we have not made as perfect a study as he has. We have used penicillin in a considerable number of cases of puerperal mastitis.

It would seem from the study that 0.51 per cent is a rather high incidence of mastitis. In our clinic, though I have not the figures, I am sure it is not quite that high. I think the more breasts are left alone the less mastitis will occur. Formerly, at the Lying-in Hospital, as soon as a patient was delivered, the breasts were scrubbed, alcohol and bichloride of mercury were applied, and they were kept absolutely clean by sterile dressings, and I have never before or since seen so many breast abscesses. The lesson to be learned is to leave the breasts alone. Do not irritate them and thus produce cracks that will permit staphylococci to enter. As Dr. Hesseltine pointed out, that is the organism you expect to find, but in some abscesses, on culture, streptococci were noted.

It is important to stress the alterations in the clinical picture of this disease as well as other diseases of the puerperal woman which accompany the use of penicillin; in fact, we must learn the history of acute puerperal mastitis all over again. These drugs alter the clinical course, as Dr. Hesseltine pointed out, and we can have pus in the breast and still have a normal temperature and normal leucocyte count. That was not the case some time ago, but it is now, and we have to take those things into consideration. Two-thirds of these mothers were found to have staphylococci in nose and throat. That is a powerful argument against a good deal of thinking of how clean are the nurseries and how clean are the places where these patients are delivered, and how important it is to segregate these patients. If these patients have virulent staphylococci in the nose and throat, we bring those noses and throats into the delivery room and spread the staphylococci.

It is important also to realize that breast abscess may have a serious general effect on the patient. When I was a resident at the Lying-in Hospital, we had one patient who was admitted with a breast abscess at 7 o'clock at night, the abscess was opened at 7:30 p.m., and she was dead the next morning. We had another patient in whom a breast abscess was opened in May, and the following July she died of general peritonitis following a perforation of an ulcer of the colon. So breast abscesses are not only local infections, but they have general implications.

Also important is the fact that the more attention paid to the general well-being of the patient, the less chance there is of having any type of infection. Careful prenatal care and improvement of the general health will reduce the susceptibility to these organisms. I do not think the organisms all come entirely from the nose and throat of the mother or of the baby.

It is just as important to look in the ward for the patient who has acne or some other type of staphylococcal skin lesions, or the nurse with the paronychia, or the intern with a boil on the neck.

I should like to have heard a little more about the care of breast abscess and about the surgical opening of breast abscess. This disease is different from any other because the pus is located in the septa of the breast. That is why you have to wait until these abscesses form. If you open them early, there is poor drainage. An abscess around the areola is easier to open than one that is away from it; the latter is very difficult.

DR. JAMES E. FITZGERALD.—Mastitis is not necessarily limited to the puerperium, as one death occurred in Chicago in a woman seven months pregnant. This patient had a bilateral suppurative mastitis which terminated fatally in spite of drainage.

I am rather intrigued by Dr. Hesseltine's results in the prophylactic use of penicillin ointment which increased the incidence of suppurative mastitis by 400 per cent. I am impressed by the low incidence of suppurative mastitis in 1927-1937 which was before penicillin and before there was much refinement of the sulfonamides. It is not reasonable to suppose that our technique in the care of lactating breasts was superior at that time.

There seems to be a marked decrease in the incidence of breast infections over a period of years, and the explanation is not forthcoming. Twenty years ago infected breasts that required surgical drainage were so common that Hillis rigged up an enormous bell jar to fit over the breast so that he could use a partial vacuum for continuous drainage. Yet in the past three years only 60 breasts have required drainage. During that time we have delivered approximately 20,000 patients. This makes an incidence of about one-third of one per cent and a considerable number of patients were delivered elsewhere, which would decrease the incidence considerably. The low incidence is not due to better technique, because nursing shortage has made this impossible. It must be remembered that practically all of these patients breast feed their babies. It is also noteworthy that these patients have been sent home very early because of bed shortage.

This makes a very confused picture and I do not believe that our good results in the past few years are due to the fact that every suspicious breast infection is treated immediately with both penicillin and sulfonamides.

I have learned from Dr. Hesseltine's paper that lactating mothers may develop mastitis, that such breasts may suppurate, and that when they do suppurate, bacteria may be cultured from the pus. I would be more impressed if I could learn how to prevent the complication.

DR. HESSELTINE (Closing).—In answer to Dr. Fitzgerald, the average for the entire period of the study, thirteen and one-half years, was 0.51 per cent. The figure for the last six months of the period was 0.55 per cent; during that time we checked every patient and deleted every patient who did not nurse or lactate during that time.

OVARIAN DYSFUNCTION IN YOUNG WOMEN TREATED WITH LOW-DOSAGE IRRADIATION

DELLA G. DRIPS, M.D., ROCHESTER, MINN.

(From the Division of Medicine, Mayo Clinic)

BEFORE 1927 at the Mayo Clinic, when a young woman confronted us with the problem of functional menstrual irregularity, we could only advise that she maintain her weight at what was normal for her on a well-balanced diet, get plenty of out-of-door exercise, and avoid nervous tension. In addition to such general measures, if we found the basal metabolic rate to be lower than normal, we would suggest raising the rate to around -3 per cent by administration of thyroid extract and maintaining it at this level for several months, hoping to correct the menstrual disturbance. Sometimes ovarian extracts were prescribed with little hope of success.

About 1925 there began appearing in the German literature reports of the use of roentgen rays over the ovaries in the treatment of the functional menstrual disturbances with benefit. In cases of amenorrhea, the menses had been re-established. Rubin¹ in New York soon reported similar results. It was decided to try this treatment at the Clinic. We used extreme caution at first, irradiating only one ovary according to the technique of Rubin.

On Jan. 1, 1927, a woman from Canada registered at the Clinic. She was 32 years of age, was 5 feet 1½ inches (about 156 cm.) in height and weighed 213 pounds (about 97 kilograms). She had been married for seventeen years and had never been pregnant. She said her menses began when she was 11 years of age, were fairly regular for eleven years, lasting three days with an amount of flow necessitating use of three napkins a day. She had had much pain with the menses from the onset. The pain was present for several days before and all during the period. From the time she was 22 years old till the time of her examination her periods had been irregular, occurring from one to eight or nine months apart, and she had not menstruated for two years when she presented herself. She complained of hot flushes.

Aside from obesity, the general physical examination revealed no abnormalities. Pelvic examination gave negative results. Her basal metabolic rate was +15 per cent and the roentgenogram of the sella turcica showed no abnormality. She was given low-dosage roentgen therapy over one ovary and was told to take 10 grains (0.65 Gm.) of ovarian extract three times a day for the same two weeks each month. Her periods began the fifth day after the roentgen treatment and occurred regularly until August, when she became pregnant. After a full-term pregnancy she was delivered of a baby who was reported by the doctor to be normal in every way, but the child died shortly after birth, of respiratory failure.

The patient's periods continued to occur regularly and, the next year, another full-term pregnancy resulted in the birth of another normal infant in August, 1929. In 1933, when we last heard from her, she said that this child was alive and well. The patient's menstrual periods had been regular for a year after the second childbirth, when they ceased again in 1930.

Our good fortune in establishing regular menses in this case encouraged us to continue to use low-dosage irradiation. It has proved the most dependable means at hand of re-establishing the menses after a period of amenorrhea and of continuing the menses regularly for a few months, a sufficient time to allow the patient to become pregnant.

Irradiation in the Treatment of Ovarian Dysfunction

Before the availability of the more potent ovarian hormones, we used thyroid extract and low-dosage irradiation for several years in treatment of the functional menstrual irregularities. In the menometrorrhagic type, administration of thyroid was helpful when it could be used, but we soon found that low-dosage treatment with roentgen rays was only a temporary help (Table I) and sometimes increased the bleeding, so we had to turn to other measures such as curettage and intrauterine administration of small doses of radium. Radium probably acted on the endometrium as well as on the ovaries, for we noted that usually the periods would cease altogether for two to six months, depending on the dosage used, and then return and be rather regular for a time. Low-dosage roentgen irradiation then came to be used almost exclusively for the amenorrheic type of ovarian dysfunction. By "amenorrheic type," we mean dysfunction in which there is a tendency to longer than normal intervals between the menstrual periods and a decrease in the flow or complete absence of menstruation.

For treatment of this type of ovarian dysfunction, we at the Clinic continue to radiate one field over each temporal region, centering over the pituitary, and two fields over the front of the abdomen, centering over each ovary. The following technique is used: 200 kilovolts, 20 milliamperes, 0.75 mm. copper and 1 mm. aluminum filters, 50 cm. distance, for five minutes. This represents approximately one-sixth of a skin erythema dose. In some cases to be described later the treatment is not given over the pituitary.

TABLE I. DATA CONCERNING PATIENTS TREATED FOR MENOMETRORRHAGIA BY IRRADIATION, 1927 TO 1940, INCLUSIVE

	MARRIED PATIENTS	UNMARRIED PATIENTS	TOTAL
<i>Treatment:</i>			
Irradiation only	5	5	10
Irradiation and estrogen	8		8
Irradiation and hormones		5	5
Irradiation and snake venom		1	1
Irradiation, snake venom and Pro-luton*	1		1
Irradiation, antuitrin S and thyroid extract	1		1
Total	15	11	26
<i>Results:†</i>			
Improved temporarily	12	7	19
Not improved	3	4	7
Periods regular	6	4	10
Periods irregular	9	7	16
Menorrhagia	6	5	11
Pregnancies (full term)	3		3
Miscarriages	1		1
Pregnancies directly after treatment	1		1

*Progesterone.
†Two years after treatment.

Clinical Observations

Among cases in which patients complained of a tendency to amenorrhea and in which they had already ceased to menstruate, we early distinguished clinically two groups—one group of patients who had no complaints aside from the menstrual irregularity and perhaps a tendency to gain weight during the periods of amenorrhea and the other group who had many complaints associated both with their periods when they had them and with the periods of amenorrhea. The symptoms of which they complained were similar to those which women experience with the physiologic ovarian failure of the early climacterium. Those cases in the first group in which symptoms were not associated with amenorrhea we thought were cases of pituitary failure, and the cases in the second group in which young women had symptoms similar to those of the climacterium we classified as cases of primary ovarian failure. Later on, in the laboratory, we had the satisfaction of substantiating our clinical impressions with determinations of the amount of gonadotropin from the anterior lobe of the pituitary and estrogenic substances in the urine.

In cases of pituitary failure, the gonadotropic hormone, as a rule, is not found in the urine and if the failure is complete, at least temporarily, no estrogens can be demonstrated. When the failure is not complete small amounts of estrogen are frequently present. In cases of ovarian failure, gonadotropic hormone is found in greater than normal amounts and estrogen may or may not be found according to the degree of failure.

Clinically, cases of ovarian dysfunction due to pituitary failure outnumber those due to failure primary in the ovaries, for pituitary function is easily disturbed by general systemic conditions, including changes in dietary habits as well as disease states, and most frequently by emotional upsets. These general systemic or psychic disturbances can effect a change in pituitary function and secondarily induce menstrual irregularities at any time during the woman's menstrual life, but the young women are more prone to such disturbances, as their nervous systems are more unstable and their food habits more irregular. Pituitary dysfunction, secondary to some general disturbance, is easily remedied if the consequent amenorrhea has not lasted long enough to bring about much atrophy of the uterus. The uterus atrophies rapidly with pituitary failure if it is complete enough to induce complete cessation of ovarian function.

In addition to this group of women who have pituitary failure secondary to some general systemic disturbance, there is a group who apparently have an endogenous pituitary dysfunction due to lack of functional development of the gland or to some disturbance of undeterminable etiology. In this type of case the history of the menstrual irregularity frequently dates back to the onset of the menses or follows parturition. It is more difficult to effect an improvement with treatment in these cases.

In cases of primary pituitary dysfunction, the basal metabolic rate is usually lower than normal and the patient tends to put on weight during the periods of amenorrhea. In pituitary failure it is considered that the ovaries are adequate but dormant and, as one would expect, when these girls have a period it is likely to be quite normal and without moulimina.

Ovarian dysfunction due to a failure which is primary in the ovaries is the result of poorly developed ovaries or retained follicle or corpus luteum cysts. Here again the menstrual irregularity may date back to the onset of menstruation or follow parturition. The regularity of the cycle seems most disturbed in the pituitary type of failure.

When pituitary function is good and ovarian function is poor, the periods tend to be more regular and, though periods may be missed entirely, moulimina are often present at the regular menstrual time. Likewise some estrogen is usu-

ally present in the blood and urine. Contrary to the general impression, the content of estrogen in the urine may be higher than normal when the pituitary is hyperfunctioning and cystic follicles are present. In these cases, endometrial biopsy reveals a persistent proliferative type of endometrium and no pregnanediol is found in the urine. There is less tendency to uterine atrophy in cases of ovarian failure, unless the failure is complete and the amenorrhea has been present for a long time.

The reason for believing that many of the menstrual irregularities complained of by the younger women have a developmental basis is that they date back to the onset of menstruation and often right themselves if the young woman can be carried along to the age of approximately 23 or 24 years, when glandular development is complete.

Study of 331 Cases

We have reviewed the histories of 430 cases of typical functional menstrual irregularities treated here at the Clinic during the years 1927 to 1941. Ninety-nine cases are not included in this study. A small group was omitted because the patients had some systemic disease (diabetes, rheumatoid arthritis, or tuberculosis) which, though it seemed well controlled at the time of the treatment, had no doubt been a factor in the initiation of the amenorrhea. The others were left out because the follow-up information was either not obtainable or was unsatisfactory, or because they were more than 32 years of age. I wished in this study to include only the younger women. This left 331 cases which have been grouped as the tables indicate.

It seemed advisable to separate the patients treated primarily for amenorrhea into two groups, those single and those married at the time of treatment. Among the married women, we were interested especially in the direct effect of irradiation on the sterility associated with ovarian dysfunction. As is well known, a high percentage of these women are sterile. We wished to determine whether treatment was worth while when the amenorrhea had been present for more than one year, so the cases of amenorrhea were subdivided again into those in which the period of amenorrhea was less than a year and those in which the period of amenorrhea was more than a year.

In the whole group of single women treated with irradiation from 1927 to 1941, inclusive, for an ovarian dysfunction of the amenorrheic type, there were 136 in all. In 63 of these, the dysfunction was considered to be primary in the pituitary and in 73 primary in the ovaries.

In 46 (73 per cent) of the group of 63 cases of pituitary failure, regular menses were re-established directly after treatment. Two patients had only temporary improvement. In the other cases the improvement continued for more than one year. The dysfunction of 9 young women, as will be noted in Table II, did not improve after the irradiation therapy, but later on the menses returned spontaneously.

In 48, or 66 per cent, of the group of 73 cases in which the menstrual irregularity was considered to be due to primary ovarian failure, regular menses were re-established. In seven, only temporary improvement was achieved. In the others, menstruation continued to be regular for one year at least. Fourteen young women who received no benefit from irradiation began to menstruate later, spontaneously.

When the period of amenorrhea was more than one year, in only about 44 per cent of the cases of primary ovarian failure was improvement noted and this lasted only three months in four cases in which irradiation only was used. In the cases of amenorrhea due to pituitary failure that had been present for more than one year, improvement was noted in about 62 per cent and temporary

TABLE II. RESULTS OF TREATMENT OF 136 YOUNG UNMARRIED WOMEN* FOR MENSTRUAL IRREGULARITY, 1927-1940, INCLUSIVE

	PITUITARY FAILURE			OVARIAN FAILURE		
	DURATION OF AMENORRHEA		TOTAL	DURATION OF AMENORRHEA		TOTAL
	LESS THAN 1 YR.	1 TO 4½ YR.		LESS THAN 1 YR.	1 TO 10 YR.	
<i>Irradiation only:</i>	19	12	31	38	23	61
Improved only 3 mo.		2	2	3	4	7
Improved for 1 yr. at least	17	7	24	24	5	29
<i>Irradiation, thyroid extract, and estrogens:</i>	20	12	32	10	2	12
Improved for 1 yr. at least	14	6	20	10	2	12
Total not improved immediately after treatment	8	9	17	11	14	25
Menses returned later, spontaneously	4	5	9	7	7	14
Total patients treated	39	24	63	48	25	73
Total improved	31	15	46	37	11	48

*Patients less than 32 years old. Average age: 22.5 years.

improvement occurred in fewer cases. This makes it evident that the sooner young women who have amenorrhea are treated, the better the chance of re-establishing and continuing the menses.

To a group of the young women treated for menstrual irregularity while single from 1930 to 1941, questionnaires were sent out in 1945. We asked them simple questions relative to their general health, the regularity of their menses, whether they had married, if they had been pregnant and, if so, how many children they had had. Fifty-five answered the questions intelligently and the results are given in Table III. Twenty-one women were still single. Twelve of

TABLE III. FOLLOW-UP STUDY OF FIFTY-FIVE PATIENTS* WHO WERE UNMARRIED WHEN TREATED FOR AMENORRHEA IN THE YEARS FROM 1930 TO 1940, INCLUSIVE; INFORMATION OBTAINED BY QUESTIONNAIRE IN 1945

	PATIENTS UNMARRIED IN 1945					PATIENTS MARRIED IN 1945				
	PITUITARY FAILURE		OVARIAN FAILURE		TO-TAL	PITUITARY FAILURE		OVARIAN FAILURE		TO-TAL
	DURATION OF AMENORRHEA†					DURATION OF AMENORRHEA†				
	LESS THAN 1 YR.	1 TO 10 YR.	LESS THAN 1 YR.	1 TO 10 YR.		LESS THAN 1 YR.	1 TO 7 YR.	LESS THAN 1 YR.	1 TO 7 YR.	
Irradiation only	2	5	3	2	12	8	2	14	4	28
Irradiation, thyroid extract and estrogens	3	2	3	1	9	2	1	2	1	6
Total treated	5	7	6	3	21	10	3	16	5	34
Improved	2	2	6	2	12	9	1	13	1	24
Not improved	3	5	0	1	9	1	2	3	4	10
Periods regular	3	5	5	1	14	7	1	16	2	26
Periods irregular	2‡	2‡	1	2‡	7	3	2‡	0	3	8
Patients pregnant						8		15	2	25
Full-term pregnancies						12§		23	3	38
Miscarriages						1		0	1	2
Patients married and pregnant within 1 yr. after treatment								4		4

*Average age of patients at time of treatment: 23.4 years.

†Before treatment.

‡One patient was having no menstrual periods.

§One patient gave birth to a monster.

these women stated that menstruation had become more regular after treatment; 14 stated their periods were regular. Seven related that their periods were still irregular, and 3 of these who were amenorrheic when treated had not had any period since treatment. Thirty-four women had married. Twenty-four of these stated their menses had become more regular after treatment; 26 reported that they were having regular periods in 1945; 25 women had been pregnant and had had 40 pregnancies. Two of these had ended in miscarriages. One patient gave birth to a monster. This long-range study of low-dosage irradiation in young women makes us feel that there is no late harmful effect on the ovaries.

As I have stated, the goal to be approached in treatment of young married women complaining of menstrual irregularity and sterility is the establishment of regular periods until pregnancy can take place. It was assumed by all these women that they were responsible for the sterility. In most of the cases the husband was not with the patient when she was at the Clinic and we have no way of knowing which was sterile. This study would be more valuable if this were known. Any young married woman who has abnormal menses and is childless feels sure she is to blame for the sterility and usually will go to any length to correct it. In the results of this study, pregnancy has been considered to have been made possible by treatment if the patient became pregnant within three months after regular menses were established. Subsequent pregnancies have not been counted.

Of one group of 62 women who were married when treated, we have sufficient clinical records (over several years in the majority of cases) so that a questionnaire in 1945 was not deemed necessary. Data concerning these patients are given in Table IV. Forty-two of the women were improved with treatment and 36 continued to have regular periods; 19 became pregnant directly after treatment, and 3 of these pregnancies were terminated early in abortion. One woman in this group had 3 roentgen-ray treatments over a period of years and pregnancy directly followed each treatment.

TABLE IV. FOLLOW-UP STUDY OF CLINICAL RECORDS OF SIXTY-TWO PATIENTS WHO WERE MARRIED WHEN TREATED FOR AMENORRHEA, 1927-1940 INCLUSIVE

	PITUITARY FAILURE			OVARIAN FAILURE*		
	DURATION OF AMENORRHEA		TOTAL	DURATION OF AMENORRHEA		TOTAL
	LESS THAN 1 YR.	1 TO 6 YR.		LESS THAN 1 YR.	1 TO 6 YR.	
Irradiation only	13	3	16	20	3	23
Irradiation, thyroid extract and estrogens	7	3	10	7	6†	13
Total treated	20	6	26	27	9	36
Improved	15	2	17	21	4	25
Not improved	5	4	9	6	5	11
DATA OBTAINED 1 TO 9 YEARS AFTER TREATMENT						
Periods regular	14	2	16	16	4	20
Periods irregular	6	4	10	11	5	16
No periods	5	3	8	9	4	13
Patients pregnant after treatment	7	2	9	8	2	10
Full-term pregnancies	6	2	8	8	5	13
Miscarriages	3‡		3	2	1	3
Patients pregnant directly after treatment	5	2	7	8	4	12

*Average age of patients: 27.3 years. Average period of sterility prior to treatment: 5.7 years.

†One patient had three treatments and pregnancy followed each.

‡Pregnancy followed treatment.

A second group of 61 women who were married when treated from 1927 to 1940, inclusive, were sent questionnaires in 1945 and reported as follows: Forty stated their menstrual periods had become more regular after treatment; 39 said their periods were regular in 1945; 26 had been pregnant; 15 became pregnant directly after the treatment; two pregnancies had terminated in abortion and one woman had had a tubal pregnancy. To 1945 the 26 women who became pregnant had had 46 full-term pregnancies, 5 miscarriages, and 2 tubal pregnancies. Additional information is given in Table V.

TABLE V. FOLLOW-UP STUDY OF SIXTY-ONE PATIENTS* WHO WERE MARRIED WHEN TREATED FOR AMENORRHEA IN THE YEARS FROM 1927 TO 1940, INCLUSIVE; DATA OBTAINED BY QUESTIONNAIRE IN 1945

	PITUITARY FAILURE			OVARIAN FAILURE		
	DURATION OF AMENORRHEA		TOTAL	DURATION OF AMENORRHEA		TOTAL
	LESS THAN 1 YR.	1 TO 7 YR.		LESS THAN 1 YR.	1 TO 7 YR.	
Irradiation only	10	8	18	14	6	20
Irradiation, thyroid extract and estrogens	6	5	11	11	1	12
Total treated	16	13	29	25	7	32
Improved	12	4	16	21	3	24
Not improved	4	9	13	4	4	8
DATA OBTAINED IN 1945						
Periods regular	14	4	18	18	3	21
Periods irregular	2	9	11	7	4	11
No periods	1	6	7	4	4	8
Patients pregnant after treatment	8	3	11	12	3	15
Full-term pregnancies	16	4	20	22	4	26
Miscarriages and ectopic pregnancies	3†	2†	5	1‡		1
Pregnancies directly after treatment	5	2	7	6	2	8

*Average age: 28.2 years. Average period of sterility prior to treatment: 4.9 years.

†Two patients became pregnant shortly after treatment.

‡One ectopic pregnancy.

In summary, of 123 young married women treated with low-dosage irradiation, 34 (27.6 per cent) had become pregnant directly after treatment. Eighty-two women stated their menstrual periods were definitely more regular after treatment and, of these, 45 had been pregnant and had had 67 full-term pregnancies, 10 abortions, and 2 ectopic pregnancies; one patient gave birth to a monster after a full-term pregnancy.

Low-dosage irradiation for dysmenorrhea with regular, normal menses was given to 24 women (Table VI); 18 were improved for six months, and 8 for at least two years. One young woman became pregnant directly after the treatment. None of these young women complained of any menstrual irregularity after treatment. Several requested repetition of the treatment which had given relief several times. The effect would usually last about six months and then treatment would have to be repeated. Fearing this repetition of treatments, we stopped advising it.

Twenty-two women who had regular, normal menses and were sterile and whose husbands' fertility had been checked and found within normal limits by the criteria used previous to the last five years (no morphologic study) were given low-dosage irradiation over the pituitary and ovaries (Table VI). Eleven received pregnancy serum in addition to irradiation and 5 others were given estrogen and progesterone in addition. Three became pregnant but only 2 preg-

nancies occurred directly after treatment. Six women complained of irregularity of periods after treatment. These were the only patients of the whole group treated with irradiation who made complaints about the treatment.

It does not seem wise to treat women for sterility alone with low-dosage irradiation. The sterility in these cases apparently is not dependent on ovarian dysfunction.

TABLE VI. DATA CONCERNING FORTY-SIX PATIENTS WHO HAD NORMAL MENSTRUAL PERIODS AND WERE GIVEN IRRADIATION FOR ANOTHER CONDITION IN THE YEARS 1927 TO 1940, INCLUSIVE

	DYSMENORRHEA	STERILITY
Patients	24	22
Average age, years	25.7	28.4
Average period of sterility, years		5.1
Irradiation only	19*	6†
Irradiation and hormones	5	16‡
Improved for 6 months	18	
Improved for at least 2 years	8	
Pregnancies		3
Patients pregnant directly after treatment	1	2

*Seven of these nineteen women had two treatments. Two women had ten treatments each.

†Three of these women had two treatments.

‡Eleven women received pregnancy serum in addition to irradiation and hormones (estrogen and progesterone).

Comment

In treatment of functional menstrual irregularities, the object is to try to establish more regular normal menses and continue these until pregnancy can take place. Pregnancy is often a stimulus to the endocrine glands involved, and the menses may continue normally thereafter, though this is not by any means always the case. One hopes with treatment also to relieve symptoms associated with the abnormal menstruation.

Of the two groups of patients who have the amenorrheic type of menstrual irregularity, the group in which pituitary failure is considered to be responsible responds best to treatment unless the atrophy of the genital tract has become irreversible. The best results are attained when amenorrhea has been present for less than six months and for this reason treatment should be begun early.

In cases of the exogenous type of pituitary failure, general hygienic measures, administration of thyroid extract, and cyclic administration of estrogens or of estrogens and progesterone are usually sufficient to bring about return of the menses.

In the endogenous type, and in any pituitary failure when the period of amenorrhea has been more than a year, such treatment is often not sufficient to bring about return of the menses, and low-dosage irradiation over the pituitary and ovaries is resorted to. It is best to establish a normal basal metabolic rate by administration of thyroid extract and to try cyclic administration of ovarian hormones (principally estrogens) for several months before giving irradiation. Frequently also, though the menses may have become fairly well regulated by administration of thyroid extract and estrogen, the married woman does not become pregnant and, provided her husband's fertility is normal, stimulation of the pituitary and ovaries by means of irradiation may bring about

pregnancy immediately or at least in a few months after treatment. It is most essential in such cases that administration of thyroid extract and cyclic administration of estrogen be continued through the pregnancy or early abortion may occur, for, when ovarian dysfunction has been the rule and pregnancy has occurred, early abortion is a common sequence. In recent years, since potent estrogens have been available for oral administration, some women who formerly have aborted several times have carried through a pregnancy with this therapy. In our cases in which we used irradiation before we had potent estrogens, we did not appreciate this, and several abortions did occur. Fortunately, however, several of these women seemed to have more regular periods after the abortion and became pregnant again carrying through the second time all right.

In the cases of primary ovarian dysfunction, thyroid extract is used when possible to stimulate metabolism. These women usually have a near-normal basal metabolic rate. Estrogens are given cyclically to maintain the pituitary-ovarian rhythm and to control the associated symptoms. Pelvic heat is also used at times to improve the ovarian circulation. If these measures fail, low-dosage irradiation is given over the ovaries only, as a rule. If the woman is not having hot flushes, it apparently does no harm to give irradiation over the pituitary also, though I doubt that any added benefit is gained. If the young woman is having no menses, low-dosage irradiation may be given at any time. If irregular menses are still present, the treatment is best given about the twenty-fourth day after the onset of a period. If it is effective, menstrual bleeding will ensue in four or five days and another period will occur again in twenty-eight days. It is well to wait three months to see the effect of a treatment. The treatment may then be repeated if the response has not been sufficient.

Before we had potent estrogens to give cyclically, we found that the effects of irradiation would cease after three or four months and treatment would have to be repeated. In recent years we have found that when we continued to give estrogens cyclically, once we had established a cycle or a regularity for a few months, the periods continued to occur regularly.

In cases of young married women who do not want to become pregnant, I never urge use of irradiation, for symptoms they may be complaining of usually can be otherwise relieved.

We do not know how the effect of irradiation is produced but from work done in our laboratory² with comparative low-dosage irradiation over rats' ovaries, it would appear to produce a congestion only, which may liberate a hormone, presumably estrin. In some way a rhythm is established, because, with irradiation alone, menses tend to be established and to occur regularly for three months at least. After that time the rhythm again becomes irregular.

Irradiation over the ovaries seems especially indicated in cases of amenorrhea thought to be due to retained corpus luteum or follicle cyst. Some gynecologists reserve low-dosage irradiation for use in these cases only. They use it when they cannot rupture such a cyst or express the corpus luteum manually. Slight nausea is often experienced after irradiation, and a few women

have temporarily lost the hair over areas where the treatment was given. These are the only side effects, and no woman to my knowledge has complained about them.

There has been much criticism of low-dosage irradiation, and especially of that centered over the pituitary, because the pituitary makes many other hormones even more vital than the gonadotropic hormones, and interference with the production and secretion of these is feared. No case in point has been reported to my knowledge.

In low-dosage irradiation for primary ovarian failure, I have not noticed any added value in treating the pituitary, but neither have there been any ill effects if hot flushes were not being experienced. The only questionable ill effects may have been in the cases of sterility and normal menses that I have mentioned.

In cases of amenorrhea of more than one year's duration, if only one method of treatment were available, I would prefer low-dosage irradiation. It has proved to be the best single method of therapy in such cases. Combined therapy has been somewhat more effective; that is, when necessary, giving thyroid extract enough to raise the basal metabolic rate to -3 per cent and holding it there, and then administering ovarian hormones, particularly the estrogenic, cyclically for three months at least before irradiation, again after treatment, and on through a pregnancy, if one ensues.

I wish to acknowledge the assistance of consultants in the Section on Therapeutic Radiology of the Mayo Clinic in this study.

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FEAR, AN IMPORTANT ETIOLOGICAL FACTOR IN OBSTETRIC PROBLEMS*

HOWARD C. WALSER, M.D., DETROIT, MICH.

IN SPITE of the fact that any ten-minute cloakroom discussion among colleagues in the specialty of obstetrics and gynecology includes mention of the vagaries of the mind and emotions of their patients, there has been no resultant study of these factors from the obstetric viewpoint. A beginning in this direction was made several years ago when the professor of obstetrics in one of our large midwestern medical schools sent one of his residents to an eastern medical school for one year's intensive study of psychiatry, but, in so far as I know, this plan has not been continued.

Most of the literature on the subject is entirely from the psychiatric or psychoanalytic approach, written and studied by psychiatrists or analysts who do not have the opportunity to see the actual working out of their theories at the bedside in the maternity hospital. The obstetrician, on the other hand, does not read the psychiatric literature and would have difficulty understanding it, if he did the reading, because of his lack of training in basic psychiatry. The result, in the main, is lack of sympathy between the specialties and inadequate understanding by the obstetrician, which makes his work more difficult for him and for his patients.

In his inaugural address as president of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons in September, 1944, Dr. Willard R. Cooke¹ took notice of this lack of correlation between the physical and emotional problems of women. While he did not attempt to relate basic psychological facts to clinical obstetric entities he did rationalize some of the less well understood peculiarities of female psychology, and went on to say that "ninety-five per cent of the severity of human suffering is mental; a great deal of the symptomatology encountered in the practice of gynecics is of purely mental origin."

The Mental Hygiene movement which began forty years ago with the express purpose of improving the care of mentally sick patients has shown a change in direction of purpose, with much more emphasis now being placed on prophylaxis and prevention. This naturally focuses attention on causes, and we are told that most adult psychoneuroses have their origin in childhood, with particular emphasis that, in the first two years of life, the causal anlage of full-blown adult emotional difficulties is laid down. Since the most important interpersonal relationship in this period of growth is the maternal-infant relationship, is it not axiomatic that, if we have an insecure, fearful, uninformed mother, the infant is bound to be affected? And is it not true also that, if the mother

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is in a chronic state of anxiety in the early period of a baby's formative years, it is very likely that the mother's state of mind must have antedated and continued throughout the period of gestation? Ignorance breeds fear and fear is the basis for chronic insecurity and an anxiety state which leads to disrupted emotional life. It is impossible to refer all harassed patients to psychiatric consultants, since there are too few psychiatrists and the added expense is often prohibitive. It is also impossible for all obstetricians to have any sort of didactic psychiatric training, and it is certainly dangerous for an untrained man to dabble with quasianalytical psychotherapeutic techniques. However, it is not too much to ask even the busiest obstetrician to make an effort to know his patients well enough to recognize the fertile soil in which seeds of anxiety have been sown and root them out or expose them at least to the fires of sympathetic understanding. An obstetrician cannot practice psychiatry, but every time he erases a fear from his patient's mind he is doing an excellent job of psychotherapy.

Much has been written of the emotional problems of the menarche and the menopause, with suggestions regarding their attempted solution in clinical gynecology. Undoubtedly, psychogenic factors play a tremendous role in the causation of dysmenorrhea, functional amenorrhea, oligomenorrhea, menorrhagia, metrorrhagia, etc., in the youthful patient, on the one hand, and may be also present in the hot flashes, headaches, dizzy spells, backache, and abnormalities of flow in the patient in her fifth decade. However, in an attempt to be concise and contained, this discussion will be limited to psychogenic factors in relation to clinical obstetric problems.

To quote Cooke again: "When a woman discovers or imagines that she is pregnant, several conflicting emotions come into play. On the one hand, there is the subconscientious satisfaction of the maternal instinct and frequently delight in the prospective advent of the baby. On the other hand, there is the basic subconscientious pregnaphobia with its conscientious exaggeration, fear of pain, fear of death, dislike of the inevitable deformity, and often hatred of the unwanted child and its father. Given such a foundation of conflict, it is only natural that the horrors of which she has heard, and of which she will certainly be plentifully informed by her female 'friends,' tend to create a psychoneurotic superstructure which is apparent in a great many cases. Tocophobia is probably responsible for most cases of motor dystocia. Fear of the unknown in labor seems to be the origin of most of the inhibitions of motor function and of the exaggeration of pain, and in fact constitutes the real difference between the primigravida and multigravida in labor."

Karen Horney² says that fear of death at delivery may be a conscientious fear or unconscientious, but that, in either case, its real origin is in the unconscious. She adds that maternal instinct as a primal urge may be counteracted by hostility impulses against the child which may play an important part in hyperemesis, premature delivery, and depressions after delivery.

J. Whitridge Williams³ described a patient who rapidly grew moribund without any known physical cause and in spite of all the usual types of stimulation. After eight hours of gradually growing worse, she was given a large dose of morphine which was followed by sleep, improvement in the pulse, and a rapid change for the better. In this instance Williams felt the sole cause of

the patient's collapse was an emotional one, and that in knocking out her psyche with drugs recovery was permitted. A busy surgeon is not infrequently confronted by a patient who informs him before necessary surgery that she is going to die. All too often she does just that, and it seems likely that it is not a case of premonition on the patient's part. It is more logical to assume that the patient is actually, though unconsciously, committing suicide.

In order to explain the causal relationships between emotional states and subjective symptoms or actual clinical problems in obstetrics, it seems wise to begin with a study of the possibility of pre-conceptional clinical entities, and of course the most common of these is infertility itself. Horney says that frigidity can be a cause of sterility as it may be based on masturbation fears. "I have damaged myself, I shall never be able to get a child." Pseudoeyesis usually results from unconscious re-enforcement of the wish for a child or on the other hand a fear of the result of extramarital sexual relations. Obstetric teaching has hesitated to mention fear as a possible cause of infertility or so-called sterility, but if one is willing to add up the twos and twos of present-day psychoanalytic knowledge and obstetric facts, the resultant fours stare us in the face. In our study of clinical problems of infertility, the following facts seem fairly well proved:

1. Most women ovulate every month between the age of puberty and the menopause.
2. Ovulation occurs about fifteen days, on the average, before the beginning of a menstrual period.
3. Many patients are conscious of definite symptoms of ovulation at this time.
4. Certain tests, such as basal temperatures, vaginal smears, and differences in electrical potential, have been used to prove the time of ovulation and this corresponds to the date of the symptoms.
5. Pregnancy results most often when coitus occurs in a close time relation to ovulation.

On the psychoanalytic side, Benedek and Rubenstein^{4, 5} have shown on several occasions that the patient is unconsciously aware of the time of ovulation. With the possibility of the patient's having conscious awareness of ovulation, fear of the pregnant state can so easily permit tiredness, headache, home duties, or a thousand and one excuses to prevent coitus during the twenty-four or forty-eight hours that might result in pregnancy. With unconscious fears and unconscious knowledge of ovulation, the mechanism, though a bit more insidious, is none the less effective. Almost 30 per cent of our patients who put themselves through the sterility clinics show no demonstrable cause for their difficulty and certainly some of these are childless because they are afraid. Dr. J. P. Pratt, in an unpublished lecture on Psychosomatic Gynecology before the Michigan Society of Obstetricians and Gynecologists, made the statement that he had experienced many more positive results by telling some of these patients that "nothing is wrong in any way so now all you need to do is go on home and get pregnant" than he has by the use of the huge array of biologic hormone preparations.

In my own practice I am certain that the occurrence of pregnancy in some six or eight patients the first month after a first visit, which included only a

simple physical examination, was the result of dissolution of this fear rather than any change that occurred during the examination.

Once pregnancy has begun, these same sterility patients get into a bit more trouble than the average, in the direction of miscarriage and premature birth. In fact, habitual abortion is a type of infertility, and here again we can logically reason out a possible mechanism. It is axiomatic that in the times of great disaster like fires, floods, explosions, bombardment, etc., premature birth and miscarriage are bound to occur at an increased rate among the affected population. This happens in women who have only been frightened by the cataclysm, as they need not show any physical injury. The great tension and fear in some manner stimulate the intrinsic and sympathetic nerve centers, Braxton Hicks contractions become labor pains, and the product of conception is expelled. Is it not true that fear is the same no matter what the source may be? Squier and Dunbar⁶ convincingly show this effect in their report of five patients who aborted as a direct result of being told that the attending obstetrician would be on vacation when they expected to be confined. And what is true of abortion is just as factual in regard to premature labor. If a planned vacation is announced in advance, certain patients will deliver considerably before their expected date of confinement.

Fear, anxiety, frustration, any or all of them, long have been recognized as the chief factors in hypertensive clinical states. Idiopathic hypertension and the different degrees of eclampsia or pregnancy toxemia have common factors. A suggested mechanism for the production of pregnancy toxemia may be a combination of two factors.

1. The patient's own nervous system effects, fear and tension with adrenalin secretion and sympatheticotonia—angiospasm, vagus depression, increased pulse rate, and hypertension.

2. The harmful effects of overeating in the anxious, insecure patient.

In my experience, the second group of patients is quite common. Beginning with the frequent meals early in pregnancy to ward off the uneasy nauseated feelings during the first three months, the patient goes on to eat herself sick. Many patients, when cautioned about an unseemly gain in weight, report that they just can't seem to control their eating because they have a constant gnawing sensation. Siddall and Maek^{7, 8} do not feel that excessive weight gain in pregnancy has much significance in predicting impending toxemia. They find that excessive gain at some period is noted in the majority of patients with late toxemia of pregnancy and was also found to occur with similar frequency in normal pregnancy. However, they did not study the incidence of toxemia in patients who have extreme weight gains. Luikart,⁹ in a much larger series of patients in whom the diet and weight were carefully controlled, is convinced that a restricted diet results in a controlled weight with less danger of toxemia, less anemia, less edema, and, in his series of 1,000 cases, the fetal mortality was $\frac{1}{6}$ that in the uncontrolled group. Luikart states that two factors control the success of his regime, namely, that the patient must understand the program and the patient must cooperate. It seems evident that these two criteria can be

stated in another way. If the physician takes the time to gain the patient's confidence and make the program clear, the patient in turn, because of the confidence and freedom from fear, has less need for the psychological stimulation and support for her unconscious yearnings and feelings of insecurity which she ordinarily deadens by frequent nibbling and overeating.

In a busy obstetrical hospital, almost every day the problem of delay in labor arises. It seems to occur in some relation to race, and very often in patients with a seemingly lower pain threshold. When we see these patients who cry out in agony and demand sedation while the contractions are weak and far apart, we have a problem which demands much of our time, considerable of our patience and sympathy, and all of our scientific interest. Why is the patient across the hall reacting so differently when many of the actual obstetric facts are so nearly alike? After all, we have always been taught that pregnancy is the biologic end point in adult female physiology. If it is physiologic, why should the process of parturition be so agonizing?

Lull and Hingson¹⁰ describe the pain pathways from the reproductive organs to the brain and speak of the pain of childbirth as being one of the most harrowing experiences a woman can encounter. Read,¹¹ on the other hand, does not agree with this. Read says, "The great intensifier of stimulus interpretation is fear. This emotion, like pain, is protective, and produces through the sympathetic nervous system a state of tension within the body. Thus we have three great evils—pain, fear, and tension. It is this syndrome which is responsible for the pain of labor . . ."

Hingson agrees on the place of fear but states it in reverse. He says, "Pain can be brought to a frightful nearness through the telescope of fear. Fear can be greatly accentuated and magnified through the microscope of pain." He also suggests that there are two methods of controlling pain.

First, the anatomic approach, i.e., by blocking pain impulses at their source as in local, spinal, regional anesthesia and caudal analgesia.

Second, the encephalic approach, i.e., by obliterating pain at its site of interpretation in the central nervous system through various forms of general, intravenous, and rectal anesthesia.

"Some measure of control is afforded by obtunding the memory of pain through the use of drugs which produce amnesia or forgetfulness. The control of fear is sometimes the more difficult of the two."

Hingson controls the pain by stopping impulses at their source. Read gets the same result by the thalamic approach with the patient acquiring the ability to relax her nervous, emotional, and physical self so that the interpretation of pain stimuli in the thalamus is less rigorous. The latter method certainly is not hypnotism, but the place of suggestion in this method of handling obstetric patients must be conceded.

However, the hypnotic state with posthypnotic suggestion has been shown by Kroger et al.¹²⁻¹⁴ to have a sphere of usefulness in gynecies. In spite of its limitations, Kroger and his associates have had very definite results in dysmenorrhea and the nausea and vomiting of pregnancy and have delivered a high percentage of their patients without memory of pain in labor. Until we have many more trained men available, most of us are prevented from following Kroger's methods.

However, Hingson also suggests that caudal block has a definite place in the treatment of hypertension in medical and obstetric cases, thrombophlebitis, Dietl's crisis, arterial emboli of the legs and peripheral angiospastic diseases.

He also states that there is no change in the force, frequency, or duration of the pattern of uterine motility under caudal analgesia. In these patients labor progresses *more rapidly*, (italics are mine) than we ordinarily would expect because of the relaxation of the cervix and perineum.

I am going to suggest that most of the clinical entities Hingson has mentioned as being influenced in some measure by caudal analgesia, in addition to rigid cervix, have certain psychogenic origins, as often demonstrated by psychoanalytic approach, and that fear can be a factor in their original manifestations. I also suggest that, with caudal analgesia, he is merely breaking up the sympathetic and parasympathetic connection with the higher emotional centers, just as surely as the neurologic surgeon does with his scalpel during sympathectomy.

All of us who are connected with the problems of the delivery room recognize the strain and uncertainty of a prolonged labor, a strain not only on the attendants in the birthroom but on the expectant mother's family, to say nothing of the patient herself. The labor pains are far apart, the fetus does not descend, the cervix does not dilate and everyone is not only anxious but tired. If the patient has been without rest for a long time she is allowed to sleep by administering a sedative and in many cases, after a few hours' rest, without too much evidence of any other change having been effected, delivery proceeds to a more rapid conclusion. Many times, with frequent strong contractions, cervical dilatation seems to be at a standstill. These are the cases in which sedation in some form seems to allow the cervix to "melt away," as we also see weak irregular contractions of almost a "false labor" type change to forceful efficient ones under small doses of hypnotics.

Why should we assume that there is some uterotropic selectivity of these drugs we use? Is it not more reasonable to assume that the cause of the delay might have been emotional? If fear can cause tenesmus of the colon and bladder, can it not cause tightness or rigidity of the cervix? If fear can cause increased adrenalin secretion, sympatheticotonia with increased pulse rate and hypertensive states, why cannot a similar origin be the basis for hypertensive toxemic conditions in pregnant patients? Why should labor pains stop completely in such a high proportion of patients when they are admitted to the maternity hospital? And why should a patient have a cessation of all pain when the doctor or nurse walks in to her room preparatory to an examination? I believe this is often unadulterated fear and that as soon as acclimatization to her surroundings is complete, progress continues uninhibited.

Conclusions drawn from the material herein presented are difficult if not impossible. Until frequent case studies correlated by parallel observation between obstetricians and consultant psychiatrists are presented, it is not wise to think of proof. However, certain impressions have been gained, and these impressions are almost incontrovertible, even in the light of our present incomplete knowledge. These impressions are as follows:

1. Fear and the ultimate ramification of its effects can change the physiology of the human organism.

2. Pregnancy and labor should be physiological processes. However, because of the complete control of the reproductive system by the sympathetic and parasympathetic nerve chains, the function of reproduction is very susceptible to emotional stimuli. Fear, leading to tension, can disrupt the reproductive function in devious ways.
3. The avoidance of the effects of fear is in the hands of the obstetrician. He should first avoid increasing his patient's fears by words or deeds or by passively accepting a situation which expresses the patient's insecurity in the slightest degree.
4. The obstetrician should actually thwart the effects of fear by establishing a rapport with his patient as quickly as possible, and he should answer all questions simply and encouragingly. He should recognize his own limitations and call in the trained psychosomaticist whenever possible.

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3001 WEST GRAND BLVD.

SPINAL (SADDLE BLOCK) ANESTHESIA IN OBSTETRICS*

G. J. ANDROS, M.D., WILLIAM J. DIECKMANN, M.D., P. OUDA, M.D.,
H. D. PRIDDLE, M.D., R. C. SMITTER, M.D., AND W. M. BRYAN, JR., M.D.
CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

ANALGESIA and anesthesia are important medical treatments to anyone who is in pain. The parturient woman is justified in her demand for relief from the pains of labor and of delivery if it can be given without endangering her life or the life of her baby. No doctor is justified in refusing pain relief to the woman in labor, and no doctor is justified in using analgesia and/or anesthesia to a degree which is dangerous to the life of the mother or the baby. The numerous methods of analgesia for labor would indicate that none is satisfactory. This is not true. There are several methods that the experienced obstetrician can use to give amnesia-analgesia to 85 to 95 per cent of the women in labor. Anesthesia for the delivery is a more precise procedure and depends entirely on the presence of one qualified to administer the anesthetic of choice.

The doctor must always remember that any interference with the normal course of labor—hypnotics, oxytocics, anesthetics—increases the hazards for mother and baby. Continuous caudal analgesia has been used by us in several hundred cases, but our own experience, as well as that reported in the literature, indicates that continuous caudal is not the optimum type of analgesia and anesthesia. It requires considerable skill and has potential dangers that cannot be completely eliminated. Spinal anesthesia has been used for many years, and although it, too, is potentially dangerous, it requires less skill in actual administration than does continuous caudal analgesia.

It was our purpose to determine the advantages and disadvantages of spinal (saddle block) anesthesia for the relief of pain in labor and for the delivery. We have demonstrated to our satisfaction that, with some training, the average physician can administer spinal anesthesia for relief of the pain of the late second stage and for the delivery, with a high degree of safety. In fact, this type of anesthesia is far safer than an inhalation or intravenous anesthetic administered by an inexperienced individual. We believe that the subcutaneous injection of 0.01 Gm. of morphine and 0.0005 Gm. of hyoscine without any repetition of the morphine but repeated injections of 0.0003 Gm. of hyoscine at 45 to 90 minute intervals can be used with safety by the experienced doctor for the relief of the pain of the first and early second stage of labor. Intermittent inhalations of nitrous oxide or ethylene gas and oxygen or a spinal anesthesia may be used for the second stage and for delivery. Our experience thus far

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with saddle block has led us to the conclusion that the qualified specialist, employing proper obstetric judgment and technique, may use this method of analgesia and anesthesia during the latter part of the first stage of labor as well, and may repeat the spinal injection in carefully selected cases.

The ideal regional anesthesia for labor and delivery could be imagined as a single-injection technique employing a small dose of an agent possessing a prolonged duration of effect and capable of being limited precisely to segments of the body between the umbilicus and the upper thigh.

It is probably with these factors in mind that Parmley and Adriani¹⁻² first carried over into obstetrics the work of Adriani and Roman-Vega³ on modified saddle block anesthesia using Nupercaine.

Present Study

This is a study of 719 cases of modified saddle block anesthesia carried out at the Chicago Lying-in Hospital between Jan. 5, 1947, and April 24, 1947. These cases represent 58 per cent of all patients delivered during this period of time.

All of the spinal anesthetics for six weeks were administered by three assistant residents whose only responsibility in the case was that of carrying out the saddle block procedure. They had had only the usual amount of training in anesthesia that is associated with the internship of one or more years plus varying degrees of experience in the Army or Navy. After the routine had been established and these three men were well trained, six other assistant residents and two physician anesthetists took part in the spinal anesthetic program. The training of all the doctors taking part in the study was under the close direction of one of us (G. J. A.) who has had an extensive experience with caudal and other regional anesthesia methods in association with R. A. Hingson.

A special anesthetic form was used on which all pertinent data were recorded with the exception of the drug used; which, together with the patient's name and number, was recorded on a separate sheet which was clipped to the special record form. One of us (W. J. D.) removed the separate sheet containing the name of the drug and arranged the special form sheets in groups of approximately 50 or 100, in all of which the same drug was used. When the study was completed, two of us (G. J. A. and H. D. P.) analyzed these various groups without knowing what drug was used. When all of the groups had been analyzed, the key was supplied by W. J. D. Similar groups were then combined and represent the basis for this paper. The data in Table I illustrate the results in various groups and show that the observations were properly made and the study carefully carried out since, in general, there is little difference for the various groups. On the other hand, there is enough variation to show the necessity of obtaining data from a large group of cases. This method of study increased the amount of work, and prevented any changes during the course of the work, but did permit, we believe, a most complete evaluation of spinal (saddle block) anesthesia in obstetrics.

The technique of anesthesia was demonstrated to us by Parmley, and was used throughout the study with minor modifications only in so far as drugs other than Nupercaine were involved. The majority of the injections were carried out with the patient in her labor bed, under the mattress of which had been

inserted board supports to prevent sagging. The patient was placed in a sitting position over the side of the bed, bending forward and supported by an assistant. The lower back was prepared with alcohol and a mercurial tincture. Local anesthesia infiltration of skin and deeper tissues was not carried out.

TABLE I. COMPARISON OF SOME DATA OBTAINED IN ANALYSIS OF VARIOUS "UNKNOWN" GROUPS OF PATIENTS

GROUP	PER CENT						
	A	B	C	D	E	F	G
Patients delivering after 60-120 minutes of analgesia	49	41	48	53	60	52	36
Patients requiring at least one postpartum catheterization	19	34	24	22	16	22	30
Patients with some postpartum headache	13	14	9	18	17	18	24
Patients with systolic blood pressure fall of 0-30 mm. Hg	82	78	88	83	87	84	83

Groups A-E each represent ± 100 patients in whom nupercaine was used.

Groups F-G each represent ± 60 patients in whom pontocaine was used.

Spinal puncture was made at the level of the fourth lumbar interspace. In case of difficulty at this point the third space was utilized. A short-beveled 22-gauge needle three inches in length was used in the majority of cases.

When a free flow of clear spinal fluid was obtained, a Luer Lok syringe containing the properly prepared solution (Table II) was attached to the spinal needle, aspiration of 0.1 c.c. spinal fluid carried out, and the solution injected rapidly. At the end of ten seconds the needle was removed, and at the end of thirty seconds the patient was placed flat on her back with a pillow under the head to keep the neck sharply flexed. The procedure was timed to be carried out in its entirety between contractions of the uterus, to prevent any abnormally high level or aberration of anesthesia which might result from spinal fluid turbulence coincident with contraction.

As soon as the patient was in the supine position, the following observations were made and recorded on the specially prepared form. The blood pressure was taken at least every five minutes for the first thirty minutes following the injection of the drug; and every fifteen minutes thereafter. Basal blood pressure was determined by regular observations throughout labor preceding the block, including one reading immediately before the induction of anesthesia. Observations of the maternal pulse rate and fetal heart rate were made between blood pressure readings. Oxygen and emergency drugs including ephedrine, Methedrine, Coramine, and (soluble) sodium amytal were kept immediately available. The patient was not moved or allowed to change position for twenty minutes after the injection.

All but seven of the anesthetics were completed with four drugs. These drugs with dosage and method of preparation with glucose are presented in Table II.

Buffered nupercaine (formerly perein) in 1:200 solution, the drug used by Parmley and Adriani, was administered to 404 patients in dosage of 2.5 mg. Premixed unbuffered nupercaine (2.5 mg./c.c. in five per cent glucose) was tried in 109 instances. These two gave statistically similar results (Table I) in our hands, and have been grouped together as Drug 1 in our analyses.

Pontocaine (tetraecaine) hydrochloride (Drug 2) was used in 115 cases. The dose was arbitrarily selected as 5 milligrams. By employing the 1 per cent solution of the drug, it was possible to create a technique for preparation with 10

per cent glucose which was identical to that for 1:200 nupercaine. This was deemed of importance by us in setting up a routine which would prevent accidental improper dosage.

TABLE II. PREPARATION OF ANESTHETIC AGENTS USED

DRUG	DOSE (MG.)	METHOD OF PREPARATION	TIME SITTING UP (SECONDS)
1. (a) Nupercaine (buffered) 1:200 sol.	2.5	Draw up 2 c.c. of 10% glucose, then 2 c.c. of nupercaine. Mix. Discard all but 1 c.c.	30
(b) Nupercaine (unbuffered) 2.5 mg./c.c. in 5% glucose		Draw up 1 c.c. of prepared solution. Use as such.	
2. Pontocaine 1% sol.	5	Draw up 2 c.c. 10% glucose, then 2 c.c. of pontocaine. Mix. Discard all but 1 c.c.	30
3. Novocain (Procaine) 20% sol.	50	Draw up 3 c.c. 10% glucose, then 1 c.c. of novocain. Mix. Discard all but 1 c.c.	35
4. Metycaine 10% sol.	33	Draw up 2 c.c. 10% glucose, then 1 c.c. of metycaine. Mix. Discard all but 1 c.c.	35

1. Nupercaine is alpha-butyloxycinchonic acid diethylethylenediamide hydrochloride.
2. Pontocaine is dimethylaminoethyl-p-N-butylaminobenzoate hydrochloride.
3. Novocain (Procaine) is diethylaminoethyl p-aminobenzoate hydrochloride.
4. Metycaine is gamma-(2-methyl-piperidino)-propyl benzoate hydrochloride.

Novocain (procaine hydrochloride) (Drug 3) and Metycaine (Drug 4) were selected as shorter-acting agents to be tested under the saddle block technique. Novocain was used in 27 cases, with an arbitrary dosage unit of 50 milligrams. One part of a 20 per cent solution was combined with three parts of 10 per cent glucose. It would be possible to use a 10 per cent solution of the drug and create a method of preparation with glucose identical to that used for 1:200 nupercaine and for pontocaine, without altering the ultimate dose of the agent.

In the use of metycaine the dose was selected as 33 milligrams. Using a 10 per cent solution of the drug, one part was combined with two parts of 10 per cent glucose. The period of time the patient was allowed to sit up after the injection of novocain and metycaine was increased from thirty to thirty-five seconds after a few cases, to obtain skin levels of anesthesia more consistently at thoracic dermatome segments nine and ten. Forty-seven patients received metycaine.

Seven additional cases received monocaine formate.* The dose of this drug used was 50 mg. in crystalline form dissolved in 1 c.c. of 10 per cent glucose. The results are included in the analysis of the entire series of cases, but it was not felt proper to attempt any detailed evaluation of the drug in view of the small number of patients receiving it. The duration of effect of 50 mg. of monocaine appeared to be comparable to that of metycaine and novocain in this series. The greatest source of difficulty in the use of the drug in our few cases was the inconstant level of anesthesia obtained. There appeared to be no obvious relation of level of anesthesia to the period of time the patient remained sitting up after the spinal injection.

*2-iso-butyl amino ethyl para-amino benzoate formate.

It will be noted that the concentration of glucose in the solution injected varied with the drug used, with the exceptions of nupercaine and pontocaine, where equal parts of the drug and 10 per cent glucose were used. In each instance, however, the solution was hyperbaric in relation to spinal fluid.

In 24 of the 719 cases (3.3 per cent) there was failure to obtain anesthesia. Fourteen of those failures were converted to successful cases by repeating the tap and injection. In the remaining 10 patients the blocks were not repeated, by preference of the anesthetist or the obstetrician in charge of the case.

In our series of 709 successful anesthetics there were 346 primiparas and 363 multiparas. The ages of the patients ranged from 18 to 42 years. Complications to pregnancy existed in 117 cases. The most common of these was upper respiratory infection, occurring 43 times. Rheumatic heart disease was present in ten patients, diabetes mellitus in three, and pulmonary tuberculosis in three. Eighteen patients had preclampsia and nineteen had hypertensive toxemia. A miscellaneous group of 21 patients had syphilis, thrombophlebitis, asthma, ulcerative colitis, condylomata acuminata, scoliosis, mild degrees of psychosis, contracted pelvis, and other unrelated conditions.

It was our predetermined policy to use only single blocks in the great majority of cases. Excluding the 14 cases receiving two taps for a single successful anesthetic, there were 65 patients who received the benefits of repeat blocks, two of these having three effective injections.

This tendency to delay the block until labor was well advanced is reflected in the analysis of the series on the basis of cervical dilatation at the time of spinal injection (Fig. 1) and for hours of labor before the block (Fig. 2). It will be noted that 42 per cent of the patients had 9 or 10 cm. of cervical dilatation (by rectal examination) at the time the anesthesia was accomplished, while a total of 43 per cent were from six to eight centimeters dilated. A significant portion of the blocks performed during or near the second stage of labor were not, however, deliberately delayed to such a point. These results include many patients who entered the hospital in the final stages of labor and others who progressed under observation more rapidly than anticipated. It was our plan to institute anesthesia at 5 or 6 cm. of cervical dilatation in multiparas and near 8 cm. in primiparas. Other strict prerequisites to saddle block, as for all methods of regional anesthesia in obstetrics, should be progressive labor, an effaced cervix, fixation of the fetal head (particularly in primiparas) and no cephalopelvic disproportion.

Fig. 2 shows that 64 per cent of our patients were in labor for more than five hours before receiving a saddle block anesthetic. Obviously, premedication with some analgesic drug was desirable in most cases. Preliminary sedation was received by approximately 65 per cent of our patients. Morphine 0.01 Gm. alone or in combination with hyoscine 0.0005 Gm., was used most commonly. Demerol 0.10 Gm., alone or with hyoscine, and sodium amytal 0.2 Gm. were other agents employed frequently. It is our impression that patients premedicated with a barbiturate exhibit less apprehension and restlessness during delivery.

In Fig. 3 we have shown that 82 per cent of the patients were under saddle block anesthesia for less than 30 per cent of their labors, with a mean for the entire group of 19.4 per cent of labor.

It was found that the usual duration of complete uterine analgesia obtained from novocain (Drug 3) and metycaine (Drug 4) was from sixty to ninety minutes, with perineal anesthesia usually lasting nearly two hours. Pontocaine (Drug 2) generally gave uterine analgesia of from ninety to one hundred five minutes, and perineal anesthesia between two and two and one-half hours. In some patients the duration of effect with each drug exceeded the average.

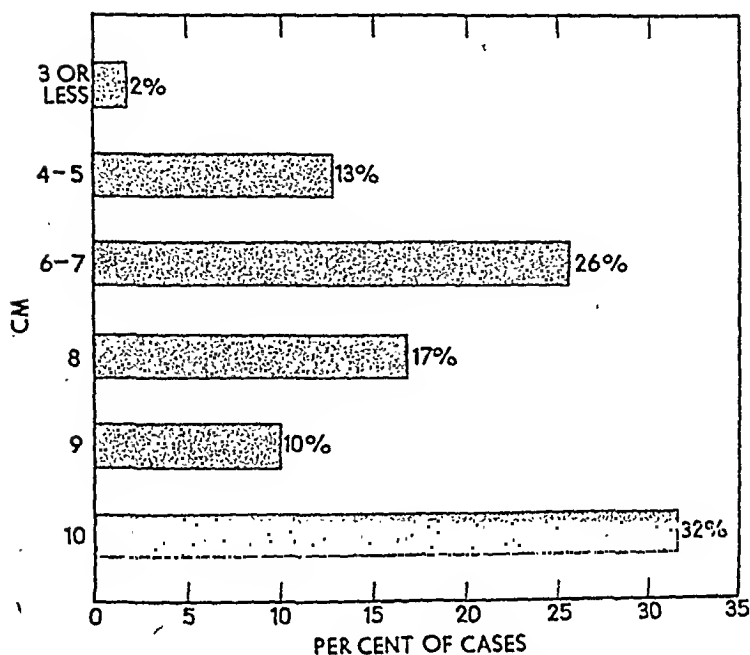


Fig. 1.—Cervical dilatation at the time of spinal injection in centimeters. By rectal examination findings, only 15 per cent of the patients were less than 6 cm. dilated at the time saddle block anesthesia was instituted, and 42 per cent were in or very near the second stage of labor.

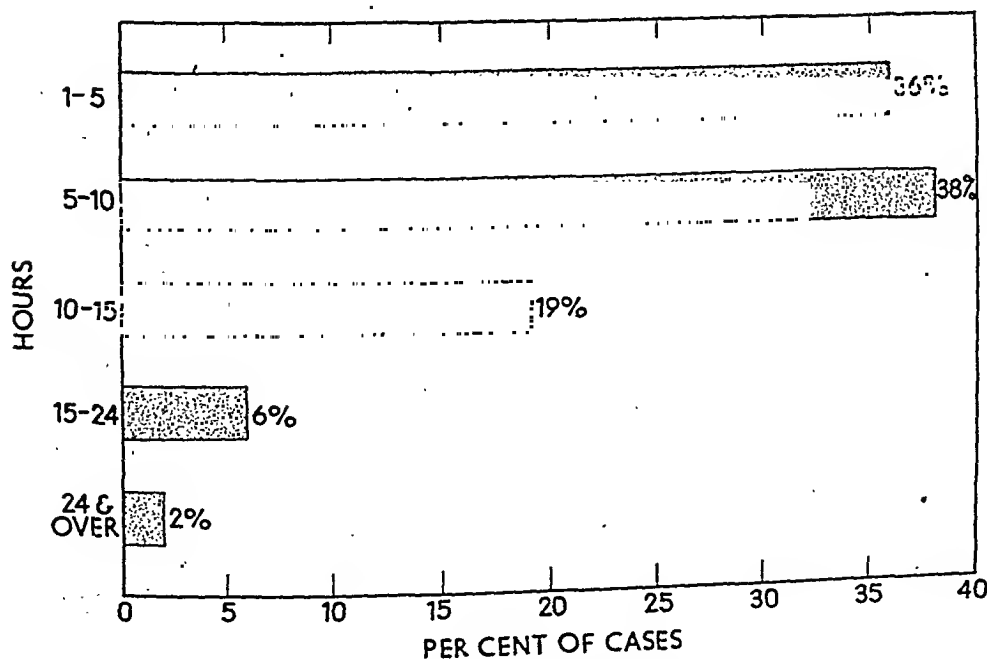


Fig. 2.—Hours of labor before spinal injection. The average patient in our series was in labor between five and ten hours before receiving the spinal injection.

We were able to observe in 100 cases the absolute duration of complete analgesia from uterine contraction pain obtained with nupercaine (Fig. 4). The mean duration was two hours and eighteen minutes. This figure is decidedly different from the average duration of three hours reported by Parmley and Adriani. Only 16 per cent of our patients in this group received three or more hours of relief with each injection of nupercaine. Where absolute duration of the perineal anesthesia was determined for the same agent, it was greater than three hours in 70 per cent of cases and greater than four hours in 42 per cent of cases.

The 65 patients who received two or three successful injections were carried under saddle block anesthesia from three hours to slightly less than nine hours when delivery was completed. Twenty patients were anesthetized less than four hours, 21 between four and five hours, and 14 between five and six hours. Nupercaine was used in the majority of these cases.

Increased incidence of failure of rotation of the occiput, delay in descent of the presenting part, and increased necessity for operative delivery procedures have been mentioned as objections to the use of regional anesthesia in obstetrics. This has been particularly evident when continuous caudal analgesia was administered early in labor. These phenomena have been thought to be the result of loss of the "bearing-down" reflex due to anesthesia of the pelvic floor and to relaxation of the pelvic sling group of muscles. We have compared the findings on vaginal examination at the time of delivery in all our patients who were managed without supplementary general anesthesia (cephalic presentations) with a control group of 2,946 patients delivered during 1944, when very little regional anesthesia was used. An insignificant increase in occiput transverse and occiput posterior positions in the saddle block group was noted.

It might be correctly assumed that any effect of regional block on the mechanism of labor would be best manifested in patients anesthetized in the first stage of labor. We have compared the types of delivery in the control and saddle block groups. The latter group has been broken down into patients anesthetized at 9 or 10 centimeters of cervical dilatation and those blocked earlier. Our comparison shows only an increase in outlet and low forceps (less marked) and a decrease in spontaneous deliveries. There were 37.6 per cent outlet forceps deliveries in the control group, 58.5 per cent in the saddle group blocked late, and 54.6 per cent in the group blocked early. In the control group 14.1 per cent of patients had low forceps deliveries, as compared to 24.0 per cent and 16.9 per cent in the respective saddle block groups.

There was no significant increase under spinal anesthesia in low forceps deliveries preceded by manual or forceps rotation, nor in midforceps procedures. All primiparas and many multiparas on our service are delivered by an outlet or prophylactic forceps with an adequate episiotomy made before the perineum has been greatly stretched by the presenting part, regardless of the type of anesthesia used.

Prolonged duration of the second stage of labor has been given as another indictment against the regional methods of anesthesia. It might be expected that the effect on the duration of the second stage would be manifested in those cases blocked at eight centimeters or less of cervical dilatation. Eighty per cent of the patients in our series who fell into this group had a second stage of less than one hour, and an additional 15 per cent of less than one and one-half hours. One patient remained in the second stage for three hours and nine minutes (negligence of resident).

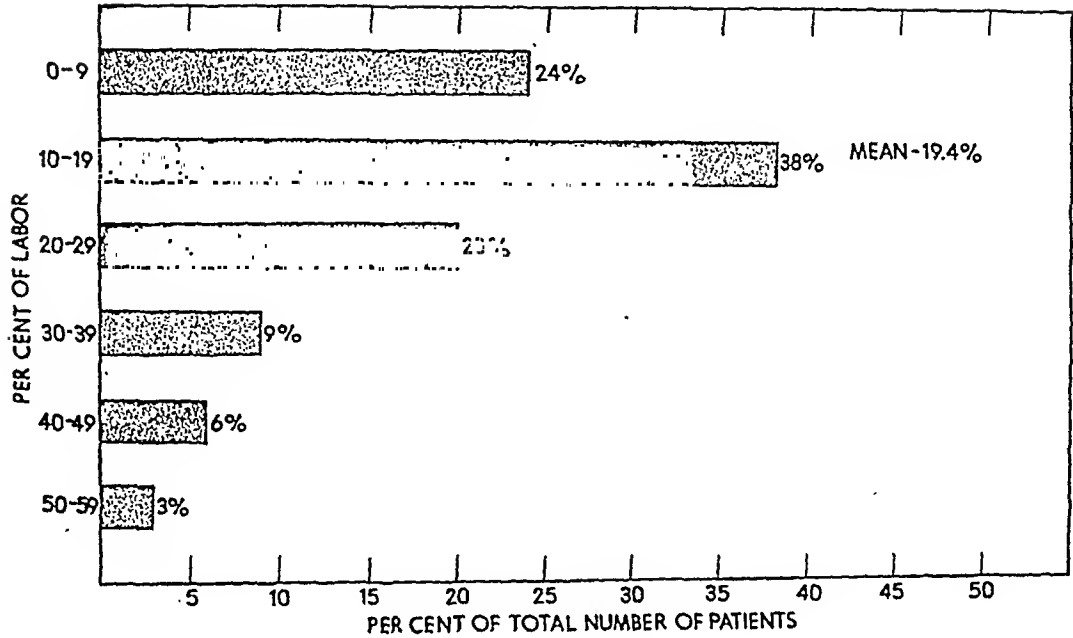


Fig. 3.—Per cent of labor under spinal (saddle block) anesthesia. Eighty-two per cent of our patients had saddle block anesthesia for less than 30 per cent of their entire labor, with a mean of 19.4 per cent of labor.

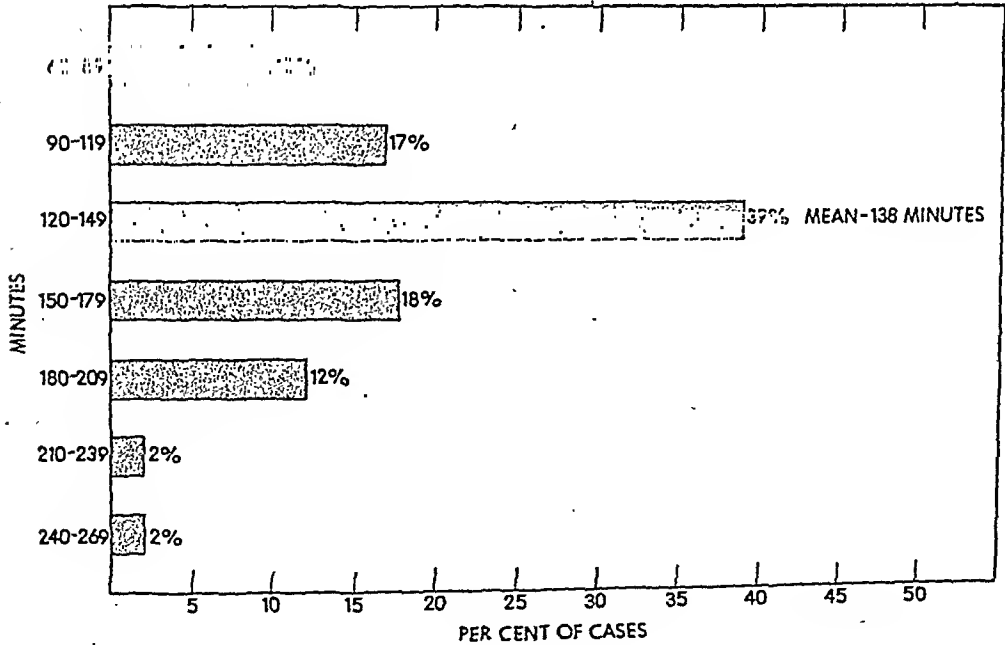


Fig. 4.—Duration of uterine analgesia to return of pain. The absolute duration of effect (uterine analgesia) of nupercaine is revealed in 100 cases who had return of contraction pain before delivery intervened.

Considering the low incidence of major operative delivery procedures necessary in our series, it cannot be said that the use of saddle block anesthesia increased significantly our operative rate. It must be emphasized, however, that we have delayed instituting anesthesia until labor was well established and we had determined the lack of significant cephalopelvic disproportion by allowing fixation of the fetal head to take place before carrying out the spinal injection.

When these factors are ignored or judged incorrectly, progress of labor may be delayed unduly and major operative intervention may become necessary.

The irritability of the uterine musculature, resulting from lack of motor paralysis in the active segment, renders extensive manipulative procedures within the uterus difficult under spinal and caudal anesthesia. We have not attempted version and extraction in any case of single pregnancy. In eight sets of twins delivered under unsupplemented saddle block anesthesia, version and extraction on the second infant was accomplished without difficulty five times. The procedure must involve working between uterine contractions, care to prevent early rupture of the membranes, and gentleness of manipulation within the cavity of the uterus. In one case where delay in attempting the version followed rupture of the membranes, the uterus contracted around the second twin, necessitating general anesthesia for relaxation.

There were twelve cases of single breech and seven cases of double breech position in our series. Breech extraction was performed fifteen times and delivery with manual aid on four occasions. We have found the extreme relaxation of the lower birth canal and of the lower uterine segment of great value in breaking up single-breech positions high in the pelvis. Again, care must be taken to work between uterine contractions and to avoid vigorous manipulation of the active upper segment of the uterus.

The management of the third stage of labor in cases delivered under gas anesthesia has included intravenous injection of 0.2 mg. Ergotrate at the time of delivery of the anterior shoulder, with a pause of thirty seconds after injection before extraction of the remainder of the body (Davis and Boynton⁴). Recently Dieckmann⁵ has shown that slow delivery of the baby (three and one-fourth minutes in primiparas) is the important factor in decreasing the time of the third stage, while the use of Ergotrate or posterior pituitary (one unit in one c.c.) serves to control the blood loss during the placental stage.

We have managed the third stage with and without the use of an oxytocic drug during the second stage. We have felt that the lack of motor anesthesia in the muscular portion of the uterus would enhance contractility and thereby hasten separation of the placenta while serving to control blood loss (Vaux and Mitchell).⁶ With no oxytocic in the second stage 89 per cent of the placentas were delivered in six minutes or less, and 58 per cent in three minutes or less. It is difficult to prevent the house staff from hurrying the delivery of the baby once the head is born.

Where ergotrate was injected intravenously with the delivery of the anterior or posterior shoulder a somewhat greater percentage of patients had a third stage of three minutes or less in duration, but there was no difference in the total percentage of patients in the two groups having a third stage of six minutes or less. Among the patients receiving ergotrate in the second stage there was evidenced a greater percentage of prolonged third stages as well as a marked increase in the number of manual removals of the placenta. This is accounted for by the tendency of the irritable uterus to contract rapidly under the influence of the oxytocic, with a trapping of the separated placenta in the

contractile portion of the uterus. Manipulation of the uterus through the abdominal wall before complete separation often results in retention of the placenta though no oxytocic has been given.

Episiotomy blood loss has been assumed by many to be greater under regional anesthesia than under general anesthesia, due to vasodilation in the anesthetized perineum. In six well-controlled primiparas delivered by low forceps extraction, episiotomy blood loss was measured by the method described by Odell and Seski⁷ of this clinic. The average rate of blood loss in the phase before delivery and in the phase of repair in these cases was not significantly different from that found by the above workers in similar patients delivered under ethylene-ether anesthesia.

Any physician who observes deliveries carried out under one of the regional methods of anesthesia cannot help but be impressed by the benefits derived by the fetus. Transplacental narcosis that is the result of general anesthetic drugs is entirely lacking. The fetus is born undrugged unless preanesthetic sedation has been excessive or injudiciously timed. In Table III we have represented the time delay in initial respiration and cry in those of our cases delivered under saddle block unsupplemented with general anesthesia, with the exception of 61 cases who received whiffs of gas only during the delivery. These are included in Table III. It can be seen that almost 95 per cent of the infants breathed spontaneously in less than one minute after delivery, which is a much higher rate than with other methods of anesthesia on our service. In only 1 per cent was respiration delayed over three minutes. The great majority of the infants took their first respiration before the entire body had been delivered.

TABLE III. DELAY IN INITIAL FETAL RESPIRATION AND CRY

TIME IN MINUTES	INITIAL RESPIRATION (%)	INITIAL CRY (%)
-1	94.5	78.5
1-3	4.5	16.5
3-5	0.2	1.9
5-9	0.4	1.5
10+	0.4	1.6

The time of the initial cry also was impressively short. Nearly 80 per cent of the infants cried in less than one minute after delivery. Of the 20 patients whose babies failed to cry in less than five minutes after birth, 12 had received morphine from one to three hours before delivery, and three others less than four hours before. Eleven of the 16 babies in this group breathed spontaneously in less than one minute. Of the remaining four babies who had not received morphine, two were of breech extraction cases and one had exhibited fetal distress before the spinal injection was given. It becomes of great importance to wipe away mucus and blood from the faces of all infants born in cephalic presentation as soon as the head crosses the perineum and to maintain a clear airway in the posterior vagina during forceps delivery of the aftercoming head in breech cases.

Six of the 709 mothers who received saddle block anesthesia with some degree of success in this series failed to leave the hospital with a living baby, an uncorrected fetal mortality rate of 0.85 per cent. Three of the six babies were stillbirths, in each of whom the diagnosis of fetal death had been made before the spinal anesthetic was administered. The condition of the fetus after delivery confirmed the accuracy of the diagnosis, giving a corrected fetal mortality of 0.42 per cent.

Summaries of the three neonatal deaths are as follows:

CASE 1.—Calculated period of gestation, thirty weeks. Weight, 1,890 grams. Respiration and cry spontaneous in less than one minute. Death on fifth day of life. Pathologic diagnosis: Resorption atelectasis, minimal pulmonary hemorrhage, jaundice.

CASE 2.—Calculated period of gestation, thirty-six weeks. Weight 2,905 grams. Respiration spontaneous immediately. Death one and one-half hours after birth. Pathologic diagnosis: Congenital urethral obstruction with massive ureteral and renal dilatation.

CASE 3.—Calculated period of gestation forty weeks. Weight 4,755 grams. Outlet forceps delivery. Moderate shoulder dystocia. Two loops of cord around neck. Respiration and cry spontaneous under one minute. Sudden cyanosis and death seven hours after birth. Pathologic diagnosis: Beginning pneumonia.

Maternal complications attributable to the anesthesia were of no serious significance. An alleged tendency for the development of abnormally high levels of anesthesia has been pointed out in the past as the principal hazard of spinal in pregnant women. This has been minimized today by development of more precise techniques, increased knowledge of the physiology of spinal anesthesia, and the use of small doses of anesthetic agents.

With the technique as first described by Parmley and Adriani and used by us without modification, 94 per cent of our patients obtained skin levels of anesthesia at either thoracic ninth or tenth segment. An equal number of patients were anesthetized to each of the two levels, and an additional 3 per cent had a level at thoracic eight. Five patients received anesthesia to thoracic five, and there were no anesthesia levels above that point. With this consistency of level not only were the potential dangers of high spinal anesthesia to mother and fetus minimized greatly, but there was very little evidence of slowing of labor due to paralysis of motor nerve elements to the active uterine segment. These generally leave the spinal cord in sympathetic nerves at high thoracic levels.

Fig. 5 indicates the effect of the nerve block on the systolic blood pressure in nonhypertensive patients. There was no significant change in 44 per cent of cases, and a maximum fall greater than 20 mm. Hg in 26 per cent. The lowest blood pressure recorded was 60/40, but there were no symptoms or signs of complete vascular collapse in this or any other patient. In the group who had a maximum fall of greater than 20 mm. Hg, no treatment was required in 70 per cent. Six per cent were given oxygen alone, 20 per cent received 25 mg. of ephedrine or 10 mg. of methedrine intravenously, and 4 per cent had a combination of the two treatments. Symptoms included transient tachycardia in 60 per cent, nausea or vomiting in 20 per cent. There was a higher incidence of significant drops of blood pressure in patients exhibiting hypertension (140/90 or greater) before the spinal injection, but in no instance did the condition of the patient prove a source of grave concern to the anesthetist or obstetrician.

Hingson⁸ states that whenever the maternal blood pressure remains below 80 mm. Hg systolic for several minutes during labor, the resting and contracting uterine tone is conceivably greater than the arterial pressure. He finds that fetal anoxia is demonstrable in almost every case where this condition is allowed to exist for five minutes or longer. The systolic blood pressure fell below 80 mm. Hg for a recordable period of time in 13.7 per cent (97 cases) of the patients receiving some anesthesia. (Hingson reported such a fall in 10 per cent of 2,457 patients receiving continuous caudal analgesia at the Philadelphia Lying-In Hospital). In our patients the fall below 80 mm. Hg was less than five minutes in duration in 51 per cent of the cases, and 10 minutes or less in

75 per cent. Fetal bradycardia below 100 beats per minute occurred in 11 instances, and all responded promptly to maternal administration of oxygen and/or the intravenous injection of a vasopressor drug. There were two other cases of temporary fetal bradycardia in our series, not associated with any significant fall in blood pressure.

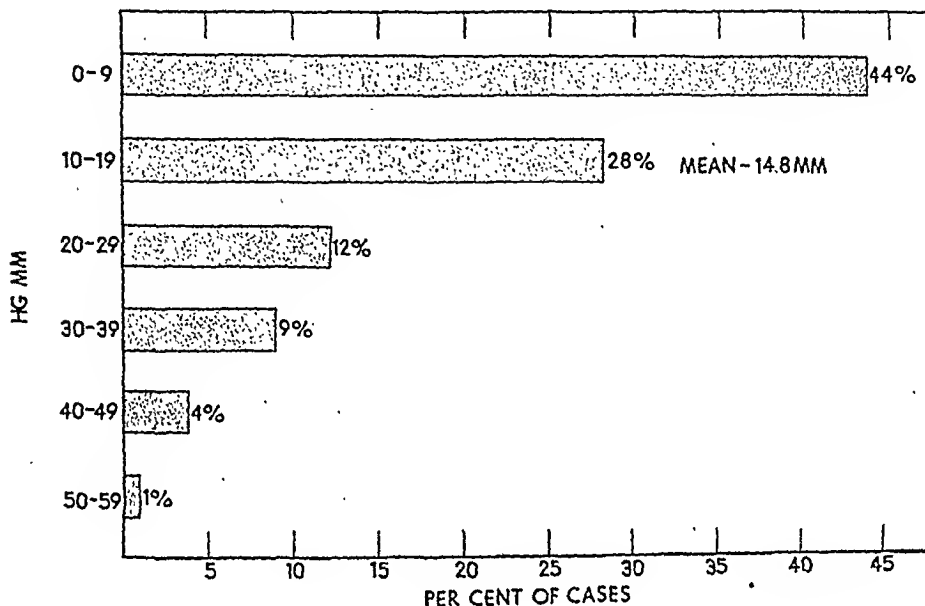


Fig. 5.—Maximum fall in systolic blood pressure in normal parturients. Excluding patients with hypertension, 26 per cent of cases had a maximum fall of systolic blood pressure of 20 mm. Hg or greater. Mean drop was 14.8 millimeters.

The incidence of postpartum catheterizations in our series was compared with a control group of 100 patients delivered with general anesthesia. An increase in the number of patients requiring only one catheterization was noticed in the saddle block cases, but little other change of significance.

Postpartum headaches in our patients proved to be a source of mild annoyance, but in no way caused us to doubt the utility of the saddle block procedure. This symptom was observed in 14.5 per cent of all patients, 10.2 per cent having "mild" headaches, 3.5 per cent "moderate," and 0.8 per cent "severe." There was no apparent difference in incidence with the various drugs used. These data were part of the information obtained by the three physicians doing most of the blocks as they made daily rounds on all patients during the entire postpartum period of hospitalization.

A headache was classified as "mild" if it did not interfere at all with the patient's activities and required no more than acetylsalicylic acid for relief. A "moderate" headache was one which required codeine or various other agents for relief and which limited in part the patient's activity for one or more days. Headaches not relieved completely by any of the usual forms of medications recommended for postspinal cephalalgia and which kept the patient more or less flat in bed were classified as "severe." There were no intractable headaches in our series. The typical time of onset was 36 to 48 hours post partum, with duration generally 48 to 72 hours. Four patients were confined to their beds for as long as five days by their headaches. It was our policy neither to restrict the patient's activity or position immediately after delivery under saddle block, nor to interfere with the general hospital regime of progressive early ambulation. This routinely begins with the patient sitting up in a chair after twenty-four hours following delivery have elapsed.

Early postspinal neurologic sequelae were not noted in this series, and to date (February, 1948) no late complications have been reported.

One maternal death occurred in this series. A 36-year-old para ii who had an uneventful saddle block anesthetic for one hour and thirty minutes died suddenly twenty-two hours after an outlet forceps delivery. She had had superficial thrombophlebitis ante partum. A massive embolism to the right heart was found at necropsy, and no contributing factors from the anesthetic were noted.

The average postpartum morbidity in the hospital is 8.3 per cent. The morbidity in the saddle block group was 2.6 per cent; however, this figure is based on only 719 cases, while the hospital figure is the average for some twelve years. It is of significance that no patient developed pneumonitis, an important cause of postpartum morbidity in winter months when general anesthesia is used for delivery.

Supplementary inhalation anesthesia was used in 96 or 13.5 per cent of the 709 patients in our series who received some benefit from the spinal injection. In 28 cases the saddle block was allowed to wear off completely and was not repeated. Fifty-seven patients came to delivery with waning spinal anesthesia or complained of severe pain during attempted delivery and these were given some supplementary gas. In 11 cases a general anesthetic of some degree was used by preference of the obstetrician, in the face of apparently adequate spinal anesthesia. The general anesthesia supplement amounted to whiffs of gas or a light ethylene-oxygen mixture for analgesia during the delivery procedure alone in 61 cases. Many of these patients had not received any (or adequate) preliminary sedation, and were extremely apprehensive during delivery. In this group the episiotomy repair was done without gas anesthesia. Complete general anesthesia for delivery and repair was given to 31 patients, and some supplement for all or part of the repair alone to four patients.

In the group of patients who received no supplementary analgesia, 84 per cent noted no discomfort during delivery or repair, 14 per cent complained of mild discomfort, and 2 per cent were moderately uncomfortable. When discomfort was present, it was generally in the form of marked pressure in the low back or in the perineum during delivery of head and shoulders of the fetus. Occasionally there was pain in the upper abdomen during forceps traction.

Elimination of grossly unstable individuals and the judicious use of pre-anesthetic medication will do much to reduce the incidence of partially unsuccessful cases in any form of regional anesthesia. Preparation during the antepartum period plus reassurance of the patient during the period of delivery assist greatly toward creating a smooth anesthetic. In inadequately sedated individuals, slow intravenous injection of 0.01 Gm. morphine after clamping of the cord will relieve restlessness from discomfort in the legs during repair of the episiotomy.

In evaluating our results objectively we classified the outcome in each case as excellent, adequate, poor or failure. The result in any case was considered excellent if there was no discomfort during labor and delivery under the saddle block and no postpartum complications of any degree. The number of patients in this group amounted to 72.2 per cent of all cases. In 20 per cent the result was adequate, indicating mild discomfort with delivery and/or minor postpartum headache or urinary difficulty. There were 6.4 per cent poor results. These patients needed general anesthesia supplement because of inadequate pain relief, or they had definite difficulties in the postpartum period. Cases in which a successful block was allowed to wear off and was not repeated were not considered as poor results for this reason alone. Failure to obtain any anesthesia occurred in 1.4 per cent of cases.

Each patient's reaction to the saddle block procedure was obtained during the period of hospitalization after delivery. In 80 per cent the response was one of enthusiasm for the method. A good reaction was elicited from 13 per cent, fair from 6 per cent, and poor from 1 per cent. There was no significant difference in the responses from primiparas and multiparas as groups.

Discussion

One of the authors, W. J. D., has had an extensive experience with various types of analgesic and anesthetic drugs in parturient women. He has seen many doctors enthusiastically endorse some new drug only to give it up for something newer a year or two later. We believe that the doctor who does obstetrics must familiarize himself with one or two drugs for amnesia-analgesia, and with a general anesthetic and one or two methods of regional anesthesia for delivery. The studies of new drugs should be left to the large clinics and only accepted by the doctor when they have stood the test of several years' use and he then has learned how to administer them.

Every parturient woman must be seen at least every 30 minutes during the first stage by an experienced intern or nurse and someone must be in constant attendance during the second and placental stages. If a drug for the relief of pain is given, the intervals during the first stage between observations must be every ten to fifteen minutes or, preferably, someone with experience must be in constant attendance.

We believe that our success with spinal (saddle block) anesthesia has been due to our insistence on meticulous attention to every aspect of the procedure. The patient is evaluated as a proper candidate and her progress in labor followed carefully. At the appropriate time the technique of instituting anesthesia is carried out precisely. Particular attention is paid to exact dosage of the anesthetic agent and to timing in positioning the patient after the injection.

During the first half hour of anesthesia the physician remains with the patient. The level of anesthesia is checked closely; the maternal blood pressure and fetal heart rate are obtained at intervals of five minutes or less. Significant drops in blood pressure are treated vigorously with oxygen and/or intravenous injections of a vasopressor drug. When the patient is ready for delivery, this is done promptly. Prolongation of the second stage of labor, for the convenience of doctor or nursing staff, particularly with the presenting part resting on the perineal floor, will increase fetal mortality under any form of analgesia and anesthesia. The placental stage is carried out in such a way as to prevent blood loss.

Our experience in this large series and in 1,800 cases subsequently has convinced us that saddle block anesthesia as we have carried it out is a safe procedure in obstetrics, and one of great value to the parturient and fetus. On the other hand, misapplication of its principles, carelessness in the technic, and neglect of the anesthetized patient will result not only in poor success but in an increased fetal and maternal morbidity and mortality. This can be said for any procedure or drug used in labor and delivery. Experience is invaluable, and must be obtained cautiously.

Summary

A series of 719 consecutive cases of spinal (saddle block) anesthesia in labor and delivery have been analyzed and the results presented in detail. The procedure has been found to be safe, simple and precise; and the degree of success has been high.

The rate of operative interference in delivery was not significantly increased.

Complications attributable to the anesthetic procedure have not been a problem.

The benefits to the fetus in early spontaneous respiration have been striking.

There has been no increase in the fetal or maternal morbidity or mortality.

We wish to thank Dr. Parmley for his kindness in demonstrating to us the technique developed by Dr. Adriani and himself.

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THE USE OF THE VAGINAL SMEAR IN A GYNECOLOGIC SERVICE*

LOCKE L. MACKENZIE, M.D., BEN B. WETCHLER, M.D., M.Sc. (Med.),
JOHN C. DuBOIS, M.D., AND THEODORE NEUSTAEDTER, M.D., F.A.C.S.,
L.M. (DUBLIN), NEW YORK, N. Y.

(From the Department of Gynecology, the New York Post-Graduate Medical School and Hospital)

THE vaginal smear technique was begun in 1940 at the New York Post-Graduate Medical School and Hospital, and has now become an important aid in diagnosis in the Department of Gynecology. The material for this study was accumulated by searching all hospital and clinic records from 1940 until 1947. Included also is a large number of smears from outside private patients of physicians on the hospital staff.

Problems in the field of vaginal smear diagnosis fell into three main groups: first, endocrine; second, miscellaneous; and third, malignancy. The largest number of smears was concerned with the first and third categories, while only a few were classified in the miscellaneous column.

In this series no smears were made as a routine measure. Each was made with a definite question in mind, and usually submitted with a specific request. In this way the study differs from certain others which have been published.¹⁻⁴ Negative results are as important as positive results—especially in the diagnosis of malignancy.

The study includes several thousand smears. Many women had repeated examinations, which accounts for the fact that there were more smears than patients. The only cases excluded were those in which there was an inadequate follow-up or incomplete histologic study.

It is evident that certain of the subdivisions reported in detail are numerically small, and in these instances no conclusions were drawn from the results. It was thought best to include these small groups, however, as they may represent a trend, and they do show the possibilities of the method and demonstrate some of the various uses to which it may be put.

Different staining techniques have been used. Recently the stain devised by Papanicolaou,⁵ and since modified slightly by him, has replaced others to a large extent, particularly in suspected cancer. At present this clinic is endeavoring to devise a more rapid staining method, and the preliminary results are satisfactory. Smears were made of vaginal, cervical, and intrauterine fluids, but in this review they have not been segregated.

1. *Endocrine*.—Some of the items included in the endocrine classification were the menopause, primary and secondary amenorrheas, the relation of the vaginal smear to the menstrual cycle and to the endometrial biopsy, and the effect of irradiation on the smear.

*Read before the Section of Obstetrics and Gynecology, the New York Academy of Medicine, April 22, 1947.

Many patients were studied during the menopause. The smear was utilized to answer such questions as: Is the patient in the menopause? Does she have evidence of ovarian function? Is she responding to treatment? Is the treatment adequate? Particularly in women who have had a hysterectomy, such information is not easy to obtain by other methods.

There is no characteristic smear found during menopause. All varieties, from the deep atrophic to the early crowded types, are seen. An attempt was made to place menopausal smears into one of two groups, the crowded or the atrophic. Without going into too much detail, a crowded menopausal smear shows large numbers of pale-staining superficial cells with large nuclei, often arranged in plaques resembling a syncytium. An atrophic menopausal smear is characterized by large numbers of deep cells. These criteria were established by Papanicolaou.⁶ When the smear was not typical of either of these two patterns, it was placed in the one it most resembled.

Seventy-six menopausal women were studied. In 55 the menopause was physiologic, and in 21 it followed surgery or irradiation. The two latter were designated as surgical menopause. In order to find out if the vaginal smear showed menopausal changes in women who were clinically diagnosed as menopausal, Fig. 1 was prepared. This shows that approximately four-fifths of the smears agreed with the clinical diagnosis. Inaccurate clinical diagnoses were responsible for some of the lack of agreement. There was no significant difference in this regard between natural and surgical menopause.

It then seemed desirable to find out whether or not there was any difference in the character of the smear depending on the type of the menopause, and Fig. 2 illustrates the findings. This shows cases of both surgical and natural menopause, and the percentage of crowded and atrophic smears. While it is apparent that the crowded type predominates in both, the atrophic type is 10 per cent more frequent in the surgical menopause. It was thought that the more severe the menopause seemed clinically, the more the smear tended to be atrophic. It was anticipated that the sudden and almost complete cessation of ovarian function caused by surgery might result in a more marked effect on the smear, and this actually occurred. Furthermore, the effect of estrogenic therapy on an atrophic menopause often made the smear crowded before it became either cornified or follicular. On the other hand, a crowded smear was never converted into an atrophic type as the result of such treatment. If these facts were correct, they should be confirmed by a study of the type of smear as contrasted with the duration of the menopause. Fig. 3 was prepared with this in mind. This shows, in this series, that there is a definite difference in the character of the smear depending on the duration of the menopause. An arbitrary time limit of eighteen months was chosen. Before this time about two-thirds were crowded, while after this period about three-fifths showed atrophy. The effect on both patient and smear of various types of medication was investigated, but the results were not included as it was thought they might entail too much detail for such a general discussion. They will be published later in another paper. The crowded menopausal type of smear was changed more quickly and uniformly into a cornified smear than was the atrophic type. Frequently, a patient's clinical symptoms cleared up before there was any alteration in the smear. Also, when treatment was stopped, symptoms tended to recur before there was any regression in the smear. This "lag" was observed in many cases, varied from one to eight weeks in duration, and must be considered in evaluating the effect of treatment.

In some of the primary and secondary amenorrheas, low dosage irradiation to the pituitary and ovaries was given, but opportunity to study the effect of this modality on the vaginal smears was afforded in only six cases. They are

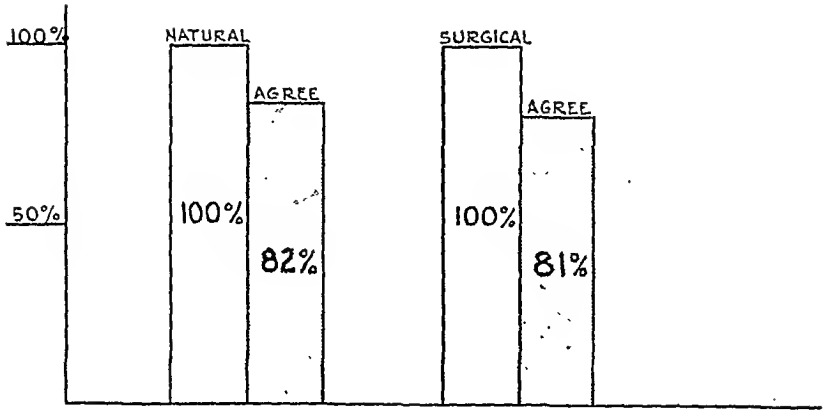


Fig. 1.—Menopause; agreement with smear.

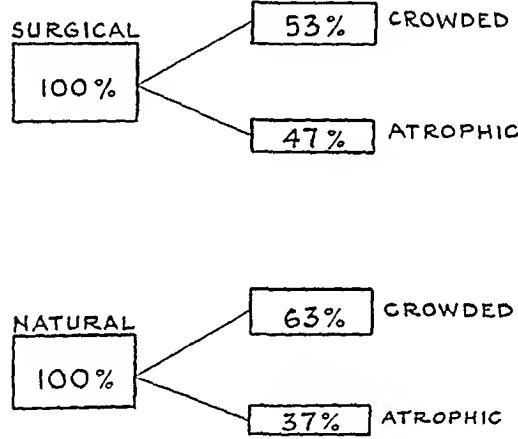


Fig. 2.—Menopause; smears which agree with diagnosis.

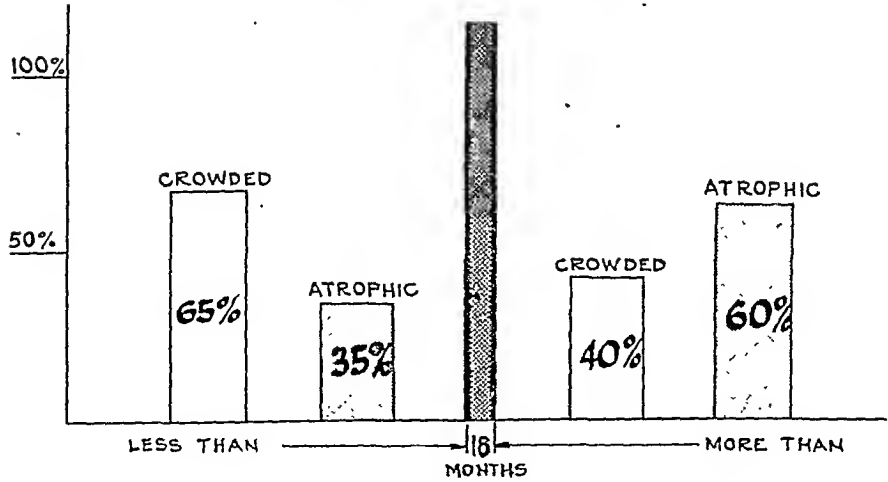


Fig. 3.—Menopause; character of smear and duration.

reported in Fig. 4, merely as an illustration of one of the phases to which this method may be applied, and no conclusions were justified.

Fig. 4 shows the results in these six cases. Five were secondary amenorrheas of various durations, and one was a primary amenorrhea. In the one case of primary amenorrhea, smears before and after therapy showed no change. No change was seen in two of the secondary amenorrheas. In another, charted as a "poor response," the smear, which was menopausal before treatment, changed to the type often seen in a secondary amenorrhea. In only two instances was a good response noted. One smear which was typical of secondary amenorrhea changed to that of a normal cycle. The sixth patient also established a normal cyclic smear and she soon became pregnant.

In a large number of instances a single smear was taken to find out whether or not it agreed with the menstrual cycle. Papanicolaou's criteria⁶ were used. The type and date of the smear were checked against the known dates of the menstrual cycle. Questions asked were: Is this a normal menstruation? Has the patient ovulated? Is the follicular phase normal? Is the luteal phase normal? Is the patient going to menstruate? It at once becomes obvious that a single smear cannot answer all of these questions. A number of complete cycles was studied, and they usually did provide adequate information, but they are not included in Fig. 5 which is based on single smears only. This shows that in more than 80 per cent of cases a single smear agreed with the known phase of the menstrual cycle. Instances in which the smear failed to agree with the cycle were clinically diagnosed as follows: two were secondary amenorrheas; one, an early menopause whose symptoms cleared up under estrogenic therapy; one was a possible pregnancy on which there was no follow-up; one was a hypothyroidism with irregular menstruation; and one a case of marked obesity. These conditions were not significantly grouped, but there were many instances in which the information gained from the examination of a single smear was important.

The determination of the presence or absence of ovulation by a single smear is greatly to be desired. A previous communication⁷ has detailed the experience of this clinic in this connection, but Fig. 6 brings it up to date.

At the time of endometrial biopsy to ascertain ovulation a vaginal smear was made. The biopsy was subsequently read and the smear diagnosis corroborated or disproved. It is seen in Fig. 6 that the smear correctly diagnosed this occurrence in about 90 per cent of all cases. Particular attention was given to the appearance of old cornification, grouping, and the generally dirtier appearance of the slide in deciding that ovulation had taken place. It should be stated that these changes may not actually be due to the corpus luteum hormone; at least, this has not been definitely proved. However, they accompany the appearance of this hormone quite regularly. Much more investigative work is essential to solve this problem. It is not recommended that a single smear be taken as a criterion of ovulation. It is merely pointed out that such a smear almost always gave the correct information.

Papanicolaou⁸ has described a smear which is characteristic of certain of the secondary amenorrheas. It somewhat resembles the pattern of pregnancy. It is typified by the appearance of large numbers of cells from the intermediate layer. An effort was made to find out if nonmenopausal amenorrheas (exclusive of pregnancy) could be differentiated from menopausal amenorrheas by means of vaginal cytology, and Fig. 7 depicts the results.

In about two-thirds of all primary and secondary amenorrheas it was thought that a differential diagnosis from menopause could be made. All varieties of smears were seen, from deep atrophy to normal-looking pictures.

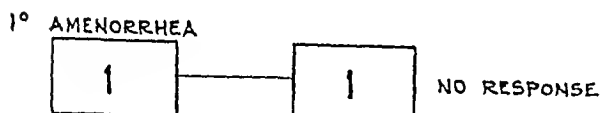
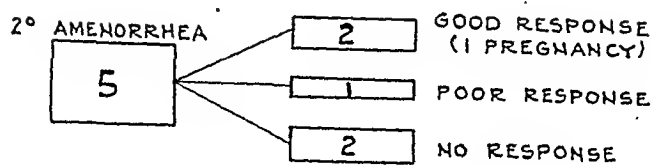


Fig. 4.—Irradiation; effect on smear.

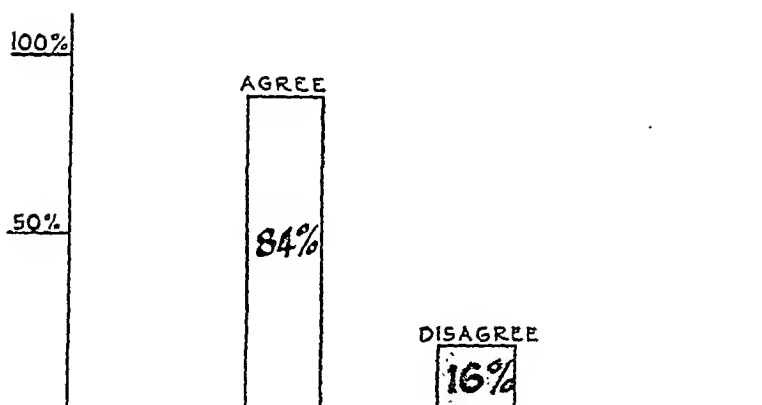


Fig. 5.—Smear and menstrual cycle.

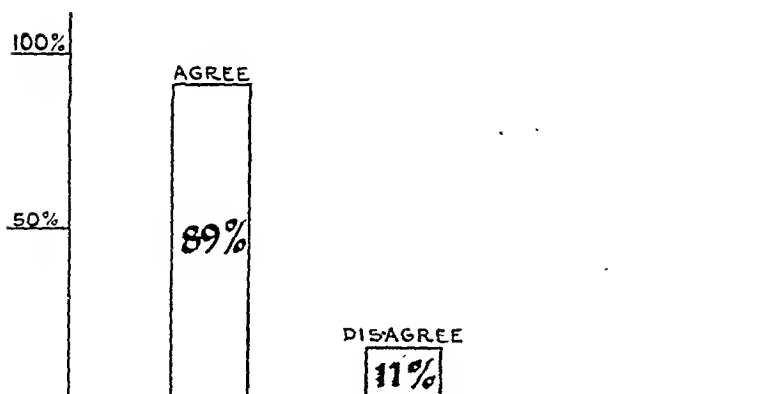


Fig. 6.—Smear and endometrial biopsy.

It was believed that this method of examination often helped to establish the prognosis. Thus, there seemed to be very little use in attempting any type of treatment for an amenorrhea when the smear showed marked atrophic changes.

In a few instances in which the clinical diagnosis was functional menorrhagia, a frequent finding was a hyperestrogenic type of smear.

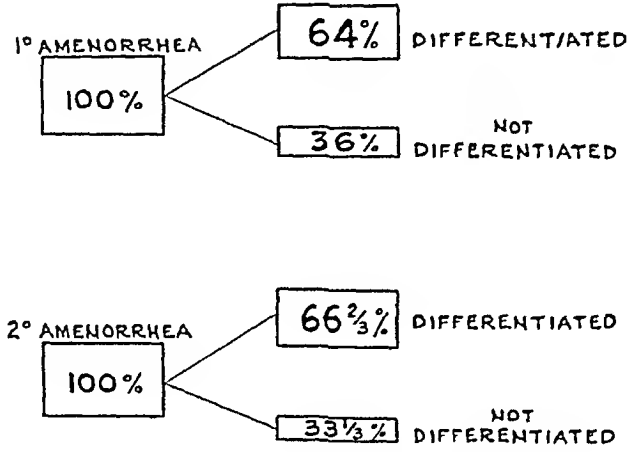


Fig. 7.—Amenorrhea (first degree and second degree): differentiated by smear from menopause

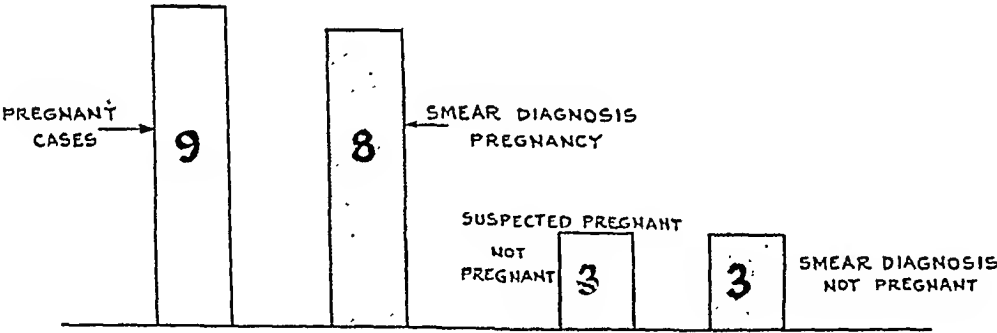


Fig. 8.—Pregnancy.

2. *Miscellaneous.*—This group is a small one, and is composed largely of cases which did not fit into either of the other two categories. It includes various types of infections, pregnancy, sterility, and certain other conditions. Some of the questions asked were: Is the patient pregnant? Has she trichomonas? What is the date of her ovulation?

In two cases of infertility of the husband, cycles were studied in the wife to determine the date of ovulation for artificial insemination. In one, nineteen inseminations were done without result; pregnancy resulted in the other from a single insemination done three days before the height of the follicular reaction. In this woman, smears taken fifteen days after conception were typically post-ovulatory, and not premenstrual.

Trichomonas were frequently found, often in women presenting no symptoms. In another large group, an excess of leucocytes was noted, yet the clinical findings showed no evidence of infection. Some of these may have been due to intercourse, but not all, and the appearance of large numbers of polymorphonuclear cells in otherwise normal smears requires further explanation.

The Post-Graduate Hospital has no maternity service, and relatively few women come solely for the diagnosis of pregnancy. However, this diagnosis was attempted in a small group, shown in Fig. 8.

Fig. 8 shows that 12 patients were referred for the diagnosis of pregnancy. Nine women were pregnant, and the smear made the correct diagnosis 8 times. The missed diagnosis occurred in a woman who was four weeks past her last menstrual period, and, although the smear looked premenstrual, the patient was pregnant at the time. Three women were not pregnant, and the smear showed no evidence of pregnancy. In a few postpartum smears, the appearance was characteristic. In one criminal abortion, pieces of syncytium were observed.

3. *Malignancy*.—Before going into detail of the diagnosis of malignant changes, it is necessary to state a few preliminaries. Smears were reported as positive, negative, and suspicious. The last diagnosis means that no definite malignant changes were noted, and the smear was considered negative. In such cases a request for additional smears was always made. In the statistical outline which follows, a smear was considered as in error if it was reported as suspicious and the patient really had cancer. This made for a rigid criterion of accuracy and accounted for some of the errors reported. Papanicolaou has described five types of smears in connection with malignancy diagnosis, number one being negative, number five unquestionably malignant, and the intermediate numbers being more or less suspicious. It was felt that the more uncompromising classification used in this study might prove an even more exacting test of the accuracy of the method. Suspicious smears were relatively few in number. At this point it should again be re-emphasized that these women were not referred for routine examination. Each was either a suspected carcinoma or definitely diagnosed as such. A few unsuspected malignancies were encountered while examining smears for other changes, but vaginal smears were not used in this series as a screening procedure, but rather as a means of diagnosis.

No attempt has been made to relate the specific grade of carcinoma to the smears. Except in general terms the type of cancer has not been correlated with the smear, as it was felt that this would involve too much detail in such a paper as this. Neither has the time element of the diagnosis by smear been charted in relation to the time of the histologic diagnosis. The smear diagnosis was nearly always made before the tissue diagnosis.

Occasionally, a squamous-cell carcinoma was diagnosed as adenocarcinoma, and vice versa. Except to mention such instances, they have not been included as mistakes, for it was felt that a confirmed diagnosis of cancer was sufficiently correct.

Generally only one question was asked: Does the patient have cancer? Recurrences after treatment were sometimes found. At times the diagnosis of malignancy has been by somewhat oblique means. One woman, with a solid tumor of the ovary, ascites, and hydrothorax was thought to have a possible Meigs' syndrome. Vaginal smears were negative, but smears from the chest fluid showed adenocarcinoma; at operation bilateral ovarian adenocarcinoma and carcinomatosis were found.

Changes following radiation therapy for carcinoma have as yet been very incompletely studied, but recent work from Boston⁹ tends to show that such changes may be of prognostic significance. Fluid from ovarian cysts has been investigated, but not thoroughly. Malignant cells in these fluids do not look as they do in the vaginal fluid, and it was felt that this means of diagnosis was of little value.

After discarding those cases incompletely followed and those in which inadequate tissue studies were made, there were 112 women who had cancer or in

whom the diagnosis was suspected. The results of the smear examination in this series is shown in Fig. 9.

In the entire group the smear diagnosis was incorrect in 11, making its accuracy 90 per cent. If the basis of comparison is a positive histologic diagnosis of malignancy, the smear diagnosis was accurate in 89 per cent.

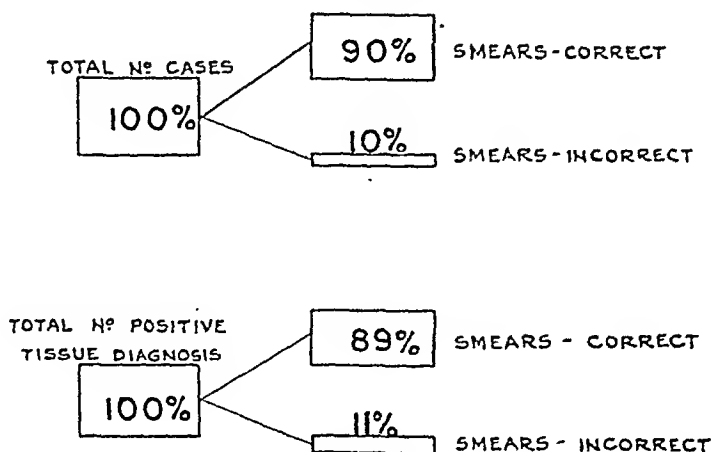


Fig. 9.—Malignancy: diagnosis by smear.

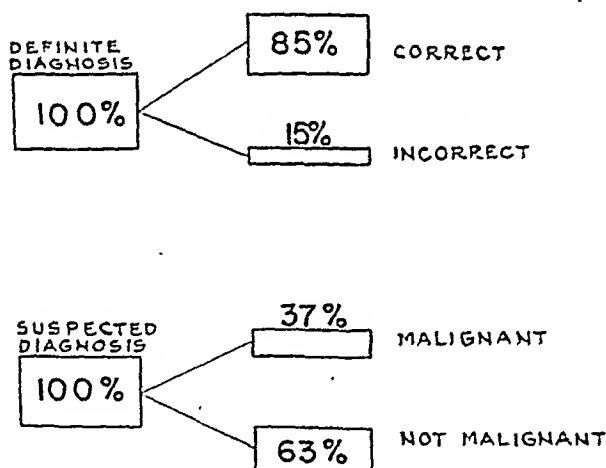


Fig. 10.—Malignancy: diagnosis clinically.

It is of special interest to scrutinize the wrong diagnoses. Seven of the 11 mistakes were false positives (6 per cent); of these, 3 were incorrectly called squamous-cell carcinoma, and 4 adenocarcinoma. Four of the 11 mistakes were false negatives (4 per cent); of these, 2 were reported as suspicious and turned out to be a squamous-cell carcinoma and an adenoacanthoma. The last 2 proved to be a squamous-cell carcinoma and a leiomyosarcoma, and both were reported as negative. Another case of leiomyosarcoma was correctly diagnosed by smear.

Two instances of adenocarcinoma were diagnosed squamous cell, and two squamous-cell tumors as adenocarcinomas. Two cases of adenoma malignum were correctly diagnosed. It appears that less difficulty was encountered in this series with the diagnosis of adenocarcinoma than with squamous-cell carcinoma, which is contrary to the usual experience. In this group all cases in which the tissue diagnosis was positive for adenocarcinoma showed malignant cells in the vaginal fluid.

Frequently a definite clinical diagnosis was made. At other times the examining physician made some such note as "rule out Ca," or "possible malignancy." Fig. 10 shows the accuracy of these diagnoses.

It demonstrates that the doctor was correct in 51 (85 per cent) when he made a definite diagnosis. In the 52 instances in which he suspected the possibility of malignancy but did not definitely diagnose it, the patient was found to have carcinoma in 19 (37 per cent). It is thus seen that the diagnosis by smear corresponds very favorably to clinical judgment.

Discussion and Summary

It may be said in general that the information derived from the vaginal smear technique is a distinct addition to our diagnostic resources. It is confidently expected that its use will be more universal as time goes on. It is not suggested that it supplant the well-established diagnostic methods such as physical examination, biopsy, and biologic hormonal assays and tests, but it is suggested that vaginal smears be used as complementary to the others, and that a proper amount of credence be placed in their interpretation. There is always danger in relying too much on laboratory tests and this applies equally to vaginal smears. It is easy to accept a negative diagnosis of malignancy and then fail to carry out the other tests which will prove or disprove it.

No method is of more than passing interest if only a few men can learn to interpret it. Unquestionably, some time must be spent in learning the normal vaginal cytology, for it is by this means alone that abnormal cells and patterns may be recognized. At the New York Post-Graduate Medical School the method is taught to matriculates and they usually become proficient in smear diagnosis at the end of their course. This series represents the individual interpretation of four doctors, all of them practicing clinicians, and none spending more than a few hours at a time with the actual study of slides. This is one factor which may be responsible for the 10 per cent of errors in the diagnosis of malignancy, most of which were made during the early years of this work.

Many problems remain to be studied, and they will be more readily solved by improvement in staining techniques, both as regards simplicity and specificity. A simple, quick, and reliable office technique for staining vaginal smears is needed. Some have been described¹⁰ but they are not yet entirely satisfactory.

As the hormonal aspects of gynecology assume greater importance, and as less reliance is placed on the curette, diagnosis by cytologic means becomes more significant. Some problems which immediately suggest themselves are: the description of a change in the smear which would be diagnostic of ovulation; further work on early pregnancy; and, possibly most important, the attempt to find a smear pattern indicative of a premalignant change.¹¹ When carcinoma is present, there is very little difficulty in finding it in the smears. At times this method seems to provide the only means—short of major surgery—by which cancer of the female genitals may be recognized. A few cases have been described in which borderline changes were noted in the smear, and in which the patient has developed leucoplakia and squamous metaplasia.¹² It would seem that every effort should be expended in this direction. The implications of such a

discovery would indeed be of the utmost importance, for, lacking knowledge at present of the cause of cancer, its early diagnosis is paramount.

The results of seven years' experience with the vaginal smear technique as used in the conduct of a gynecologic service have been presented. Types of clinical problems which the smear may help to solve have been discussed. Correlation has been detailed throughout with the clinical findings. Endocrine disorders, miscellaneous conditions, and malignant disease were studied. A short dissertation on some of the future problems incidental to continued use of this method has been given. The great importance of finding a method to diagnose premalignant changes was stressed.

Conclusions

1. Diagnosis by vaginal smears represents a substantial increase in gynecologic knowledge.

2. The technique is particularly useful in evaluating endocrine disorders in women.

3. The diagnosis of malignancy of the female genitals can be made in a high percentage of cases and the method should be more widely used for this purpose.

4. All efforts should be directed toward an attempt to establish a smear criterion of premalignant change.

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PREINVASIVE AND INVASIVE CARCINOMA OF CERVIX UTERI

Pathogenesis, Detection, Differential Diagnosis, and the Pathologic Basis for Management*

EDGAR R. PUND, M.D., J. B. NETTLES, M.D., J. D. CALDWELL, M.D., AND
H. E. NIEBURGS, M.D., AUGUSTA, GA.

(From the Department of Pathology, University of Georgia School of Medicine)

THE term "preinvasive carcinoma" denotes a carcinoma which is confined to the natural surfaces and which does not penetrate the underlying stroma. We deprecate the use of the term "precancerous" for these lesions and believe that "precancerous" should be used to designate morbid changes which, from past experience, are known to be followed by cancer in many, but not all instances. In precancerous lesions a cancer cannot be detected, but is to be anticipated and therefore prevented, as for example vulval kraurosis and lingual leucoplakia. On the other hand, we believe that the preinvasive cancers are obviously neoplastic, and will ultimately invade unless they are eradicated.¹

The criteria for the diagnosis of preinvasive cancer are based upon cytologic alterations from the normal, a change of functional epithelium to a vegetative type. The nuclei are larger than normal, vesicular and hyperchromatic, of irregular size, and the nuclear-cytoplasmic ratio is increased. Mitotic figures, sometimes bizarre, are readily demonstrable. Differentiation is either absent or incomplete. In the cervix uteri the preinvasive carcinomas not only involve the external surfaces, but also extend into the glands of the endocervix. This extension may be mistaken for invasion; however, careful study of several sections will minimize this error.

An invasive carcinoma is one in which the epithelium breaks the barriers of the restraining stroma and thereby gains access to vascular channels which may be permeated by neoplastic cells to undetectable distances and distributed as embolic implants to remote parts of the body.

Pathogenesis of Carcinoma of the Cervix Uteri

In a recent publication,² one of us (E. R. P.) with Auerbach described the pathogenesis of carcinoma of the cervix. The study of additional material has enabled us not only to corroborate, but to extend these observations.

Cervical squamous cell carcinomas usually begin in the endocervical canal at the junction of the stratified squamous and columnar epithelia. The source of these cancers is probably the endocervical basal cell³ whose location corresponds to that of the early cancer. Three stages of cervical cancers have been described: (1) preinvasive carcinoma; (2) covert invasive carcinoma; (3) overt carcinoma.²

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The Preinvasive Carcinoma.—An incidence of 3.9 per cent of preinvasive carcinoma has been found in our laboratory from a study of serial blocks from 1,200 surgically removed cervixes.² The proximity of this incidence to that of the incidence of recognizable cancer of the cervix implies that the majority of cancers of the cervix are preinvasive in their incipency. From the initial focus, possibly foci, the neoplastic cells spread laterally, vertically, and into the glands. Vertical extension is usually upward, but occasionally the growing cells displace to a less extent the normal stratified squamous epithelium. Lateral extension frequently involves the entire circumference at the external os.

The average age of the forty-seven patients with preinvasive carcinoma previously reported was 36.6 years.² We have now observed sixteen additional cases and the average age of the entire series of sixty-three patients is 37.7 years. In addition to those cases in which the entire cervix was examined we have observed preinvasive carcinoma in sixty-six biopsies. The average age of the patients in which the diagnosis was made from biopsy is 40.8 years (Table I). The difference of three years is significant. Preinvasive cancers are usually asymptomatic, and cancer was not suspected in our series of surgically removed cervixes. On the other hand, biopsies are usually performed on cervixes suspected of having a neoplasm or in patients with symptoms. It is therefore possible that the biopsy was not representative of the whole neoplasm, and only included that part of the neoplasm which had remained preinvasive. It is also possible that preinvasive carcinomas may have escaped detection in material from the younger age group because the focus may have been so small as not to have been included in the specimen. We have repeatedly observed small foci of cancer which could be detected only by serial blocks. Preinvasive carcinomas can only be diagnosed microscopically, and in our series we have been unable, by gross examination, to suspect the existence of these incipient cancers.

Covert Invasive Carcinoma.—Ultimately the preinvasive carcinoma becomes invasive after a variable period of latency.¹ The invasion occurs either from a large surface of the endocervix or from a single focus. The early invasive carcinomas are not visible on vaginal examination, and are therefore denoted as covert invasive carcinomas. In addition to the series of eight cases which were reported previously,² we have examined four more recent cases and have discovered five in our files. The average age of these nineteen patients is 44.2 years (Table I). The extent of these tumors varied from minute foci of invasion,

TABLE I. AGE INCIDENCE OF PREINVASIVE AND COVERT CARCINOMAS

		YEARS					TOTAL	AVERAGE AGE
		20-29	30-39	40-49	50-59	60+		
Preinvasive carcinomas of cervix from hysterectomies or total cervixes	No.	6	33	16	4	1	60	37.7
	Per cent	10	55	26.7	6.7	1.7		
Preinvasive carcinomas from biopsies	No.	6	30	13	5	6	60	40.8
	Per cent	10	50	21.7	8.3	10		
Covert invasive carcinomas	No.	0	5	9	2	1	17	44.2
	Per cent		29.4	52.9	11.8	5.9		

which were detected only in microscopic sections, to tumefaction of the entire cervix without, however, penetration of the vaginal surface. According to the information which we received with the specimen, the surgeon was unaware of the presence of carcinoma in sixteen instances. In three the neoplasm was judged to be sufficiently early to warrant hysterectomy, and in one of these the neoplasm was so advanced that a section of one ureter was included in the specimen.

Our belief that the covert carcinomas pass through a preinvasive phase is supported by the observation that a border of neoplastic epithelium, which is confined to the natural surfaces, is commonly observed in sections from serial blocks of the involved cervixes. The difference in the average age of the two groups lends additional support. Speculation on the length of time cancerous cells might remain in situ has usually been reckoned in years,⁴ and, according to our two series, this period of latency may average 6.5 years.

The Overt Cancer.—We have observed only two early carcinomas which were limited to the vaginal surface of the cervix, and we therefore conclude that the great majority of cervical cancers arise from the junctional endocervix and do not become manifest until there is definite penetration and ulceration of the vaginal surface of the cervix.

The average age of 100 consecutive patients with frank carcinoma of the cervix which was confirmed by biopsy was 49 years. It therefore appears that the majority of cancers of the cervix become obvious only after a period of time averaging five years after the onset of invasion and eleven years after incipiency. Clinical cancer of the cervix means advanced cancer.

Detection and Classification

The overt carcinomas of the cervix are readily suspected by vaginal examination and confirmed by biopsy. The covert invasive carcinoma in its late stage may also be suspected because of the firmness of the cervix and pericervical induration. The presence of ulceration of the portio, induration, and fixation are, however, signs of advanced cancer. In its early stages and sometimes even when advanced, a covert carcinoma may not be suspected. We have observed one specimen of supracervical hysterectomy in unsuspected carcinoma where the line of excision traversed the carcinoma. In several other instances the covert carcinoma was so far advanced that the condition of the patient was worsened rather than bettered by blind hysterectomy. It is therefore imperative that diagnostic biopsy of the cervix and curettage of the endocervix as well as the body of the uterus precede major surgery on the uterus.

There are no signs of preinvasive and early invasive carcinoma and, until ulceration ensues, symptoms are absent. Concentration of effort should be directed toward the detection of preinvasive carcinoma because therein lies the greatest opportunity for cure. Various investigators have demonstrated the value of the cervical and vaginal smear technic of Papanicolaou for detection of cancer,⁵ however the final diagnosis usually depends upon microscopic study of biopsied material.

It is important that biopsies be selected to include the junction of the squamous and columnar epithelia, and due allowance must be made for displacement of this junction when ectropion and pseudocerosions are present. Furthermore, it should be emphasized that the existence of preinvasive carcinoma is frequently not detected by single biopsies, in fact, in our series of studies of serial blocks there were instances when only one or two of several blocks revealed cancerous epithelium. This is one probable reason for the differential age incidence of preinvasive carcinomas in the cervixes from serial blocks and from biopsies (36.6 against 40.8) and between serial blocks of surgically removed cervixes and our earliest and most recent material when only two blocks of cervix were routinely sectioned (36.6 against 39.6).

Because invasion frequently occurs from a single focus which may not be included in the biopsy, the cancerous epithelium would then appear to be confined to the natural surfaces. Therefore a differentiation should be made between the preinvasive and the covert invasive carcinomas. We therefore recommend the following procedures. When a biopsy of the cervix proves the presence of a preinvasive carcinoma, the endocervix should be curetted. If the

biopsy is obtained under general anesthesia, curettage of the endocervix and endometrial surface should be done at the same time, and preferably the material should be submitted to the laboratory in separate containers. If the biopsy is not performed under general anesthesia, then, after the diagnosis has been made, the patient should be subjected to a curettement before starting treatment (Figs. 1, 2, and 3). We are now hopeful of obtaining sufficient endocervical curettings at the time of the biopsy without general anesthesia, but our experience in this endeavor is limited. We are in accord with the observations of Schiller, Knight, and Meyer that the examination of endocervical scrapings is important in the detection of early cancer.⁶



Fig. 1.—Preinvasive carcinoma found in cervical biopsy from a Negro woman, aged 29 years. Note how the carcinoma follows the natural surfaces and extends into the mouths of the glands. Endocervical curettage recommended. See Fig. 2.

Curettings should be washed momentarily in water in order to luke the blood and thus leave behind the residue of tissue. The tissue should then be transferred to normal saline or to the fixing solution. This important step enables the pathologist to select all or representative fragments of tissue. In our laboratory curettings are submitted from the operating room in a solution of normal saline. We wash the specimen in a beaker of tap water. Much of the blood is laked, the fresh clots imbibe fluid and swell so that incorporated tissue is easily removed and the mucus swells and can be readily identified. The residue of tissue is fixed in 10 per cent formaldehyde.

We have also had limited experience with the cervical smear technique of Papanicolaou⁷ in detecting carcinoma in routine examinations. At the present time we have had positive films from five patients in whom a preinvasive carcinoma was detected by biopsy. In one of these patients with a positive film, a section of cervix and endocervical curettings were obtained at the same time. The three sections from the cervix did not reveal carcinoma, but in the endocervical curettings there were two shivers of recognizable cancerous epithelium. If the curetting of the endocervix is carefully performed, one should be able to determine the presence or absence of invasion, and thus distinguish between preinvasive and covert invasive carcinoma.

Choice of Treatment

It would be presumptuous in this paper to discuss the relative merits of radiation and surgery in the treatment of invasive carcinoma of the cervix. In our local department of cancer, radiation has been the treatment of choice. It is also generally recognized that the cure rate of early cancers of the cervix which are treated with radiation approaches 100 per cent.⁸ We, therefore, prefer to recommend radiation for the covert invasive carcinomas and for the



Fig. 2.—Endocervical curettings from same patient as Fig. 1. Note the sliver of cancerous epithelium, and compare with the detached fragment of metaplastic squamous epithelium. The presence of uninvolved endocervical tissue indicates lack of invasion. Hysterectomy with preservation of ovaries recommended. See Fig. 3.

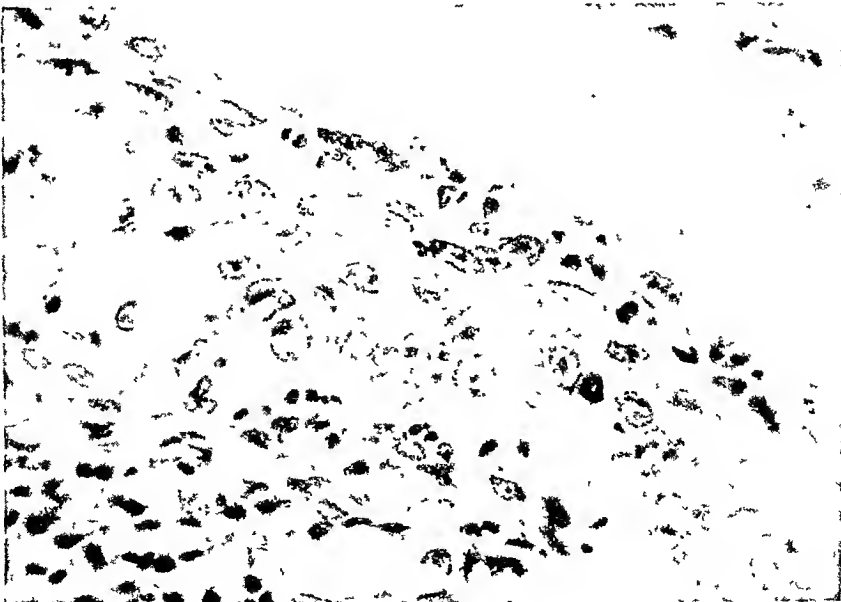


Fig. 3.—Small area of preinvasive carcinoma detected in only one of seven blocks from cervix after total hysterectomy. One ovary removed because of corpus luteum cyst.

overt carcinomas. Radiation, however, is sometimes followed by annoying and occasionally serious complications, cystitis, proctitis, endocervical strictures, pyometra and rarely fistulae. Furthermore radiation castration with its attendant symptoms frequently poses a medical problem especially in the younger age group. We now recommend total abdominal hysterectomy in cases of proved preinvasive carcinoma with preservation of the ovaries in the young. Because the average age of patients with preinvasive carcinoma is between 36.6 and 37.7 years, we deem it important to preserve the function of the ovaries.⁹ It should, however, be again emphasized that this radical departure from the usual treatment should be reserved only for patients with preinvasive carcinoma, and the precautions outlined above must be adopted to determine the presence or absence of invasion. The surgeon, too, should approach each case as an abdominal exploration and, before the uterus is removed, careful palpation must determine the absence of fixation of the cervical segment or other evidence of invasion. We, therefore, issue this caution: If invasion is thought to be present the uterus should be left in place and, because radiation will be subsequently used, we recommend surgical castration at this time. This will remove immediately the hormonal activity of the ovaries and will antedate radiation castration by only a few days.

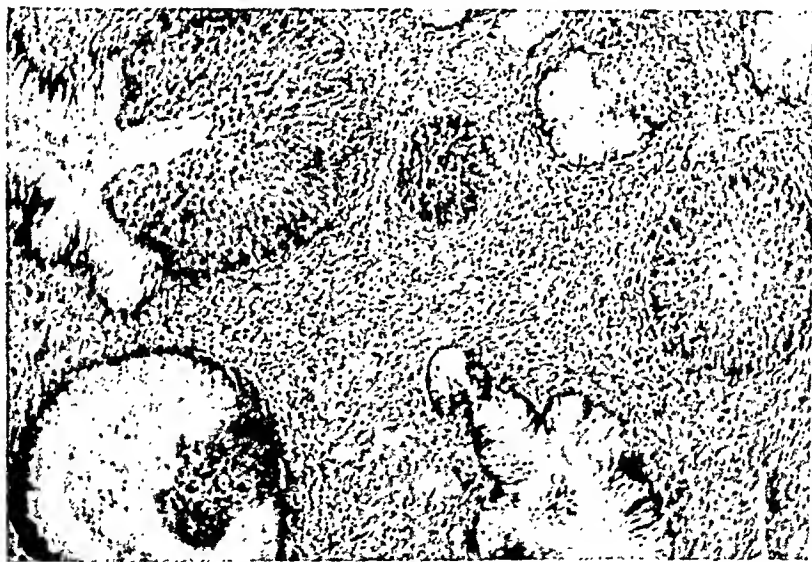


Fig. 4.—Cervical biopsy from white woman, aged 32 years. Note the presence of preinvasive cancer in several deep glands. No carcinoma was found in curettings. Subsequent total hysterectomy revealed a circumferential preinvasive carcinoma.

Measures, more conservative than hysterectomy, have been effective in the treatment of preinvasive carcinoma. We advise against cauterization and conization for two reasons, firstly, the carcinomatous epithelium is frequently found deep in the glands (Fig. 4) and, secondly, the epithelium which remains behind has been subjected to the same cancerogenic agents, whatever they may be, as the cancer-bearing area. We are also opposed to amputation of the cervix, because we have observed extension of the cancerous epithelium high up in the endocervix. In a recent case a preinvasive carcinoma was found in an amputated cervix. In the specimen from subsequent hysterectomy, seven weeks later, a preinvasive carcinoma was observed which involved the entire circumference of the cervical stump. In surgical removal of the uterus one is assured of removal of the entire area of carcinoma. In these incipient cancers there is

little probability of lymphatic extension because the stroma is not penetrated and the negligible risk of leaving the ovaries and ligaments would be counterbalanced by the preservation of ovarian activity.

Summary

The majority of squamous cell carcinomas of the cervix arise within the endocervical canal at or near the external os, therefore biopsies should include this area.

Cervical squamous cell carcinomas may be classified into three groups; preinvasive, covert invasive, and overt invasive cancer. Each group represents a stage of development over a period which averages eleven years.

Preinvasive carcinomas, the incipient cancers, are asymptomatic and can only be detected by microscopic examination.

Preinvasive carcinomas have been detected by examination of vaginal and cervical smears followed by microscopic examination of biopsies and endocervical curettings.

It is necessary to differentiate preinvasive carcinomas from covert invasive carcinomas.

The presence of a covert invasive carcinoma may not be anticipated and therefore a biopsy of the cervix and curettement of the endocervix should be a routine procedure before subtotal or total hysterectomy.

Total hysterectomy is recommended for *proved* preinvasive carcinomas, and ovariectomy is not necessarily indicated.

Appreciation is extended for Figs. 1, 2, and 3 to Lt. Col. J. M. Blumberg, U.S.A., Oliver General Hospital, Augusta, Ga.

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SPECTROSCOPIC DETECTION OF HEMATIN IN THE PERIPHERAL BLOOD

An Aid to Diagnosis of Ruptured Tubal Pregnancy

FRANK E. WHITACRE, M.D., HARVEY D. LYNN, M.D., AND
DEMPSIE B. MORRISON, PH.D., MEMPHIS, TENN.

*(From the Department of Obstetrics and Gynecology and the Department of Chemistry of
The University of Tennessee College of Medicine)*

THE term ectopic pregnancy signifies a gestation in any location outside the uterine cavity, but this discussion deals only with those occurring within the Fallopian tube. Before rupture, the diagnosis is seldom made. There is usually a history suggestive of early pregnancy, which, with irregular bleeding, makes one suspect ectopic pregnancy or threatened abortion. A tender mass located on one side of the uterus, cramplike pain, fever, and leucocytosis are usually present. After rupture, the history of early pregnancy with irregular bleeding and the occurrence of a sudden, sharp pain, followed by collapse, are characteristic of the condition. Cullen¹ finds that a bluish discoloration in the region of the umbilicus is helpful in diagnosis, but this sign is not constant. The differential diagnosis between abortion and ectopic pregnancy is of the utmost importance in the treatment of these conditions. Abortion occurs with the greatest frequency between the eighth and twelfth weeks of gestation, while tubal pregnancy may first manifest itself from the fourth to the sixth week. The bleeding in tubal pregnancy is first uterine in origin, resulting from decidual separation, which usually indicates death of the fetus in the Fallopian tube. The bleeding is usually moderate in amount and often chocolate colored. The passage of a decidual cast has been overemphasized as this is relatively rare, for usually the decidua breaks down and comes away as a part of the dark, bloody discharge. The bleeding in uterine abortion is often quite profuse and bright red in color.

In tubal gestation, the pain is usually stabbing in character, rarely colicky, and often referred to the affected side. It may be associated with a feeling of faintness or vomiting, as the result of peritoneal irritation. The pain in abortion is cramplike and rhythmical, resembling menstrual cramps. On examination in cases of ectopic pregnancy, an adnexal mass may be felt on one side of the uterus, which is semifluctuant. If there has been free bleeding in the cul-de-sac, on palpation one will feel a soft, boggy mass, which is usually tender. The uterus will be slightly enlarged and distinctly softened. In uterine abortion, the uterus will be enlarged to a size to correspond to the period of amenorrhea, and the adnexal region will usually be found negative to palpation. The cervical os is often partially dilated. Absolute diagnosis may rest upon examination of the uterine contents, which would show chorionic villi and decidua,

in the case of intrauterine gestation, but only decidua in the case of ectopic pregnancy. Puncture of the cul-de-sac or colpotomy is a frequent aid in diagnosis. In arriving at a diagnosis, the Aschheim-Zondek or Friedman test is of value only when it is positive. If it is negative, however, the possibility of ectopic gestation is not ruled out. The hormonal test becomes negative following the death of the ovum, and the separation of chorionic tissue from the tubal wall. Moreover, a positive test does not rule out the possibility of an intrauterine gestation.

Spectroscopic Detection of Hematin in the Peripheral Blood

When one surveys the various reports in the literature concerning the diagnosis and treatment of ectopic pregnancy, the results are found to be uniformly good. After supporting blood volume, the treatment of ectopic pregnancy, whether ruptured or not, is always surgical. It is common to report success in the treatment of this condition, but it is rare, indeed, to find a report showing the number of operations performed when the diagnosis was in error.

In these situations, pelvic inflammation, with or without abscess formation, appendicitis, normal intrauterine gestation, or no changes at all may be found on operation when expecting to find ectopic pregnancy. It is clear that more accurate means of diagnosis are necessary. With this in view, we are trying to make more certain of the presence or absence of extravasated blood in the peritoneal cavity.

Often a patient is under observation because of vaginal bleeding, low abdominal pain, fever, anemia, and leucocytosis in the presence of a pelvic mass. The differential diagnosis may rest upon the possibility of a pelvic abscess, hemorrhage into a cyst, appendicitis, intrauterine gestation with pelvic inflammation, or ectopic pregnancy with bleeding into the abdominal cavity. It is in such instances that additional aids in diagnosis are of value. The identification of hematin in the blood is a procedure in this direction. This was suggested to us by Dr. Isadore Snapper, formerly of the Peiping Union Medical College.

The appearance of hematin in the blood stream is not specific for ectopic pregnancy. It is significant of bleeding into a body cavity. The hemoglobin released by abdominal hemorrhage hydrolyzes and liberates hematin which is absorbed into the blood. The appearance of hematin is thus characteristic of hemolysis from various causes.

Schumm² in 1912 first devised a method of testing for hematin in the blood. The present procedure is a modification of his original work. When blood is liberated into the peritoneal cavity, clot formation takes place within a few minutes, except in abnormal blood states, such as hemophilia. Enzymes are released which bring about lysis of the clotted blood cells. When hydrolysis occurs under the influence of the enzymes, hemoglobin breaks down into its two constituents of globin and hematin. The globin is absorbed and utilized by the body as any other protein. Hematin, an iron porphyrin compound, is also absorbed into the blood stream, where it is adsorbed by the plasma proteins. It is thought that hematin is introduced into the blood by way of the lymphatic system.

Hematin may be detected by means of the spectroscope, although it gives a weak spectrum. However, the addition of a reducing agent to hematin in the presence of plasma proteins will form a reduced hemochromogen. This gives a strong spectrum consisting of two bands. A strong narrow band is located at 558 millimicrons on the spectroscope, and a fainter wide band at 527. The first band at 558 is especially characteristic.

If oxyhemoglobin is present, a narrow strong band will appear at 577 and a wider band at 545. The addition of the reducing agent transforms the oxyhemoglobin to reduced hemoglobin, which gives a wider fainter band at 555 and its usually not seen.

If oxyhemoglobin and hematin are present, the addition of the reducing agent leads to the disappearance of the two bands of oxyhemoglobin (conversion to hemoglobin with its wide faint band which has been mentioned) and to the appearance of the two bands of hemochromogen.

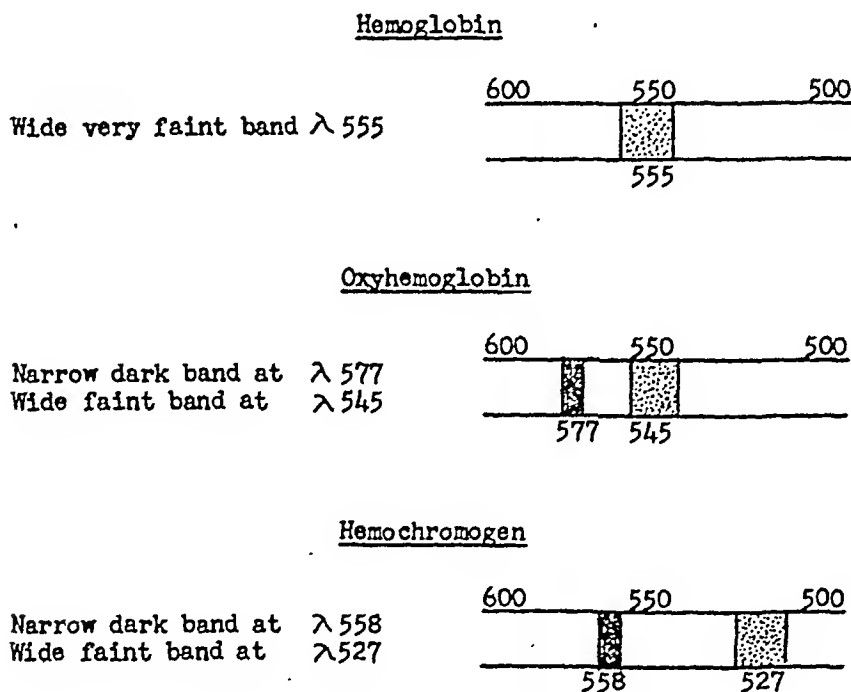


Fig. 1.—Appearance of the spectrum bands.

Technique.—Five to ten cubic centimeters of oxalated venous blood is centrifuged at 1,800 revolutions per minute for ten minutes. The supernatant clear plasma is withdrawn into a clean dry test tube and examined with the spectroscope for band visualization. A Schmidt and Haensch hand spectroscope as suggested by Wendel³ for methemoglobin determinations was used. A few drops of a solution of ammonium sulfide⁴ as the reducing agent are then added, and the spectrum re-examined for new specific band formation and disappearance of previous bands.

Fig. 1 shows the various bands of hemoglobin, oxyhemoglobin, and hemochromogen as they appear on the spectroscope. The presence of oxyhemoglobin

will depend on the amount of hemolysis that occurs when blood is drawn for testing. As can be seen, a strong band of oxyhemoglobin at 577 may be confused with a strong band of hemochromogen at 558. With the addition of the reducing substance, oxyhemoglobin is converted to reduced hemoglobin. The wide faint band of hemoglobin at 555 is not readily seen. However, an excess of oxyhemoglobin will, on conversion, form a strong reduced hemoglobin band which may mask the reduced hemochromogen spectrum. It is, therefore, essential to avoid excessive hemolysis due to trauma in drawing and handling the blood before testing.

Case Reports

The following are a few case histories to illustrate the clinical application of this test.

CASE 1.—M. F. C., a 22-year-old multigravida, entered the hospital with a tentative diagnosis of incomplete abortion at ten weeks. Her symptoms dated back three weeks. She had lower abdominal pain, a 5 cm. pelvic mass, anemia, slight fever, leucocytosis, and vaginal bleeding. The test for hematin in the blood was positive. Laparotomy revealed an old ruptured right tubal pregnancy with early lithopedian changes and about 100 c.c. of old blood in the pelvic cavity.

CASE 2.—M. E. W., a 32-year-old multigravida, had symptoms for nine days prior to admission suggesting incomplete abortion of fourteen weeks' duration. She had slight fever, anemia, leucocytosis, abdominal pain, a soft 7 cm. mass in the left cul-de-sac, and vaginal bleeding. Two cul-de-sac aspirations failed to reveal blood. Hematin testing was positive on two occasions. Laparotomy revealed an old ruptured right tubal pregnancy, with about 200 c.c. of clotted old blood.

CASE 3.—J. H., an 18-year-old nulligravida, was admitted to the service with the tentative diagnosis of ectopic pregnancy of three weeks' duration. She had fever, low abdominal pain, vaginal bleeding, anemia, and leucocytosis. The test for hematin was negative. The patient responded to medical management and was discharged with the diagnosis of acute salpingitis.

CASE 4.—G. C., a 25-year-old multigravida, was admitted with the diagnosis of ruptured ectopic pregnancy. She was in shock and presented the findings of acute intra-abdominal hemorrhage. A positive test for hematin was obtained. Laparotomy revealed a ruptured right ectopic pregnancy with about 500 c.c. of blood in the peritoneal cavity.

CASE 5.—M. E. Q., a 17-year-old nulligravida, had symptoms for three weeks prior to admission for a possible ectopic pregnancy. The test for hematin was negative. The patient responded to therapy for pelvic inflammatory disease and was discharged as improved with this diagnosis.

CASE 6.—L. B., a 38-year-old multigravida, had symptoms of vaginal bleeding, pelvic pain, and fever for six weeks prior to admission for incomplete abortion or ectopic pregnancy. The test for hematin was negative. A few days later placental tissue was passed, and the diagnosis of incomplete abortion was confirmed.

CASE 7.—W. S., a 26-year-old multigravida, was admitted to the hospital with the diagnosis of ectopic pregnancy. She had vaginal bleeding, pain, a mass in the left adnexa, anemia, and leucocytosis. Hematin testing was negative. Dilatation and curettage of the uterus established the diagnosis of endometrial hyperplasia.

CASE 8.—M. S., a 20-year-old nulligravida, was admitted in shock for ruptured ectopic pregnancy. Her findings included bleeding, pelvic pain, delayed menses, marked anemia, and leucocytosis. The test for hematin was negative. The patient responded to supportive measures and was discharged with the diagnosis of acute pelvic inflammatory disease.

CASE 9.—J. J., a 36-year-old multigravida, was in shock when admitted with a diagnosis of ruptured ectopic pregnancy. She had vaginal bleeding, pelvic pain, anemia, and leucocytosis. Hematin testing and cul-de-sac aspiration were negative. She was discharged after treatment with the diagnosis of uncontrolled diabetes mellitus and severe acidosis.

CASE 10.—R. R., a 39-year-old multigravida, had findings suggestive of a ruptured ectopic pregnancy. She was in severe shock. Hematin testing was positive. The patient expired despite restorative measures prior to operation. The diagnosis was confirmed at autopsy.

CASE 11.—V. R., a 26-year-old nulligravida, had sudden pelvic pain and fainted six hours prior to admission with a diagnosis of suspected ruptured ectopic pregnancy. Hematin testing was positive. Laparotomy revealed about 300 c.c. of fresh and clotted blood in the peritoneal cavity, coming from a bleeding ruptured ovarian follicle.

CASE 12.—S. H., a 27-year-old white secundigravida, was admitted to the hospital with a tentative diagnosis of old ruptured ectopic pregnancy. The patient had amenorrhea for six weeks followed by marked right lower quadrant pain and vaginal spotting of blood for four days prior to admission. She also had slight fever, leucocytosis, and marked anemia. There was a 5 cm. soft to firm mass in the right cul-de-sac. Hematin testing was negative. Laparotomy revealed a retroperitoneal mass extending into the vagina. There was no ectopic pregnancy.

CASE 13.—L. L., a 31-year-old Negro multigravida, was admitted to the hospital with a history of amenorrhea for one month followed by vaginal bleeding of one day's duration the next two months. There was lower left quadrant cramping for three days prior to admission but no bleeding. There was no anemia or leucocytosis. Examination revealed a firm, irregular, movable mass extending to the umbilicus. There was a separate, soft, tender mass extending into the left cul-de-sac. A diagnosis of myomas of the uterus with pelvic abscess was made. Hematin testing was positive. A cul-de-sac aspiration following this revealed blood. Laparotomy revealed a ruptured left tubal pregnancy with myomas of the uterus.

CASE 14.—This 29-year-old Negro nullipara was admitted with a tentative diagnosis of retained secundines and pelvic abscess. The patient had amenorrhea for two months, followed by vaginal bleeding and pain for one month. Dilatation and curettage were done elsewhere for an incomplete abortion. Examination on admission now revealed the uterus to be soft and slightly enlarged. There was a 7 cm., tender, soft mass on the left, but no bulging in the cul-de-sac. The Hogben pregnancy test was positive. Hematin testing was positive. Laparotomy revealed an old ruptured ectopic pregnancy.

We must report four failures in our series. In one instance, hematin testing was negative when used as an aid in the differential diagnosis between ectopic pregnancy and an ovarian cyst. The patient went into shock shortly after the blood for testing was drawn. Laparotomy within a few hours revealed a recently ruptured ectopic pregnancy. We attribute the negative test to the assumption that the ectopic gestation had not ruptured at the time of testing.

In another instance, a patient with ruptured ectopic pregnancy was admitted to the surgical service. The only blood available for testing was that in the blood bank three days after it had been drawn.

The third case involved a patient with a ruptured spleen. Blood for hematin testing was obtained after the patient had received about 3,000 c.c. of intravenous fluids in efforts to combat shock. The test was negative. Laparotomy revealed the splenic rupture.

The fourth patient entered the hospital because of vaginal bleeding. Examination revealed bulging in the cul-de-sac, and on aspiration a slight amount of thin, brown fluid was obtained. Hematin testing was negative. At laparotomy a 5 cm., firm, encapsulated mass filled with 50 to 75 c.c. of clotted blood was found. No fetus or placenta was seen. Pathologic examination showed ghost villi in the tubal remnants, and a diagnosis of old ectopic gestation was made.

Comment

Up to this time the spectroscopic test for hematin in the peripheral blood has been carried out on 100 patients in whom the diagnosis was confusing. There were 73 Negro and 27 white patients in this series, and their ages varied from 15 to 62 years. A résumé of the conditions encountered in this series is shown in Table I.

TABLE I

Threatened abortion	18
Incomplete abortion	20
Pelvic inflammatory disease	10
Tubal pregnancy with intra-abdominal bleeding	10
Complete abortion	7
Pregnancy with acute pelvic inflammatory disease	4
Myoma with pelvic inflammatory disease	2
Low implantation of placenta	1
Septicemia with acute endometritis	2
Abdominal phlebitis	1
Ruptured tuboovarian abscess with peritonitis	3
Retroperitoneal mass	1
Threatened premature labor	1
Pelvic abscess	2
Pelvic inflammatory disease with peritonitis	4
Bleeding follicle of ovary	1
Pulmonary embolus	1
Tuboovarian abscess	4
Stab wound of stomach	1
Abdominal pregnancy	1
Hyperplastic endometrium with bleeding	1
Bleeding ulcer of stomach	1
Cerebral hemorrhage	1
Ruptured spleen	1
Ovarian cyst with infection	1
Pregnancy with pyelitis	1
Total	100

All of our patients with positive hematin tests have been operated upon. We have found no false positive tests, and all patients with positive tests had at least 100 c.c. of blood in the abdominal cavity. In all cases with negative hematin tests, with the exception of the four mentioned above, the subsequent course of the patient has suggested other diagnoses than those involving intra-peritoneal hemorrhage.

The appearance of hematin in the blood stream is contingent upon several factors, and each of these may be sources of error. Clot formation is important in allowing enzymatic activity to break down the red blood cells with the liberation of hematin. Should this mechanism be faulty, there will be little or no hematin for absorption. Hemoglobin injected into the peritoneal cavity and absorbed as such will give negative hematin testing. The amount of blood loss is important also. We have been able to detect hematin in the blood of dogs within ninety minutes after injection of as little as 30 c.c. of heart blood into the peritoneal cavity. This small amount will give a positive test for about twenty-four hours. In severe hemorrhage, with the patient in shock, and for a variable period up to several days thereafter, several factors come into play and may alter the effects of testing. There is constriction of blood vessels with ischemia of the capillary bed.⁵ The total blood flow may decrease to half the normal value.⁶ There is a marked and rapid compensatory hydremia in an effort to support blood volume.⁷⁻⁹ Activity of the patient is another factor influencing the findings.¹⁰ These variables may alter absorption of hematin into the blood, in addition to causing sufficient dilution to make the test weak or negative.

We also make use of cul-de-sac aspiration and other means of diagnosis in suspected ectopic pregnancy with hemorrhage. Although intra-abdominal bleeding is usually reflected in the blood count by secondary anemia and leucocytosis, we have found that not too much reliance can be placed on the count. There have been several cases in which there was little or no anemia, and no leucocytosis. In addition, other types of bleeding and other conditions will produce similar blood pictures. Cul-de-sac aspiration is of decreasing value as a diagnostic procedure after the clot has become organized and free fluid is being absorbed.

Summary

An aid to the diagnosis of the extravasation of blood into a body cavity by means of the spectroscopic detection of hematin (reduced hemochromogen) in the peripheral blood is herein described. This is especially applicable to the diagnosis of ruptured ectopic pregnancy. A summary of the 100 patients upon whom we have carried out this test is reported. There were four failures, but there were no false positive reactions.

There are few laboratory tests that supplant clinical experience and judgment, and in this instance we are only exploring the possibility of an aid in diagnosis. At this time this report can only say that the theory and results coincide, and that we hope to perfect this technique further so that it may become a valuable laboratory procedure in the diagnosis of intra-abdominal accidents.

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THE DURATION OF LABOR: MEAN, MEDIAN, AND MODE

TRENT BUSBY, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, Johns Hopkins University and Hospital)

THE figures cited in textbooks, and ordinarily taught, for the duration of labor are eighteen hours in primigravidas and twelve hours in multiparas (Stander, DeLee-Greenhill, Beek). These are mean or average values, calculated simply by adding up the total hours occupied by all labors in a large series and dividing by the number of labors. Although mean or average figures are often valuable, it is well known to statisticians that they may sometimes be very misleading in that, under certain circumstances, they may not yield typical and truly representative values. Let us consider, as an extreme example, a community of 300 families, made up of a hamlet of 290 families, surrounded by 10 country estates each occupied by a millionaire. If the incomes of the families in the hamlet ranged from \$1200 to \$2600, as shown in Table I, and those of the wealthy group were \$50,000 each, the mean or average income would be \$3230—obviously a figure which is not at all representative of a typical family in the community. While this is an exaggerated and artificial example, it helps to recall that extreme values, which lie far outside the usual run, may so distort the mean or average of a series of observations as to render it quite meaningless.

TABLE I. CRUDE EXAMPLE SHOWING HOW A FEW EXTREME VALUES IN ANY SERIES TEND TO DISTORT AVERAGE OR MEAN FIGURES

NUMBER OF FAMILIES	INCOME OF EACH FAMILY	TOTAL INCOME
50	\$1,200	\$60,000
100	1,500	150,000
80	1,600	128,000
20	1,800	36,000
10	2,100	21,000
20	2,400	48,000
10	2,600	26,000
10	50,000	500,000
300		\$969,000
Average income—\$3230; Median income—\$1550; Modal income—\$1500		

When, in any series of variate magnitudes, a few of the values lie far outside the range of most of the values, the median and mode of the series may be more representative and informative figures than the mean or average. The median for any series of observations, it will be recalled, is the center value above and below which fall exactly half the individual values. It is particularly useful as a measure of central tendency in a series in which it is desired to suppress the influence of extreme or unusual values. By the mode of any series is

meant the value which shows the greatest frequency of occurrence, it being assumed that seriation provides a reasonably smooth frequency distribution. In the above example, the median may be taken as \$1550, while the mode is obviously \$1500. Clearly, either of these figures is much more representative of the income of the typical family in the community mentioned than is the mean of \$3230.

It is the purpose of this paper to report figures on the mean, medial, and modal duration of labor in 15,533 consecutive cases of parturition which occurred at the Johns Hopkins Hospital between Jan. 1, 1937 and Dec. 31, 1945. In this series, there were 758 cases in which either the duration of labor was unknown, or cesarean section was performed. These were discarded, leaving 14,775 cases which were grouped according to race and parity as follows:

	<i>White</i>	<i>Negro</i>	<i>Total</i>
Primiparas	4243	3278	7,521
Multiparas	4227	3027	7,254
	<u>8470</u>	<u>6305</u>	<u>14,775</u>

The criterion used for the onset of labor was regular, painful uterine contractions observed by the patient. This entails, of course, a certain source of error, but in the main such errors would tend to counterbalance each other. In the present analysis only the total duration of labor will be considered.

The calculated mean or average durations of labor for the above groups are as follows:

	<i>White</i>	<i>Negro</i>
Primiparas	13.04 hours	15.15 hours
Multiparas	8.15 hours	10.27 hours

Fig. 1 shows the frequency distribution curve of 4243 labors in white primiparas together with the perpendiculars indicating the mean, median, and modal durations of labor for this group. It will be seen that the curve is not the symmetrical type of normal frequency distribution, but is skewed to the right by reason of a small number of extremely long labors; in other words, by a few values which lie far outside the range of most of the values. Actually the limit of this curve would be 118 hours—the longest white primiparous labor in this series. The median duration of labor for this group was found to be 10.59 hours—almost $2\frac{1}{2}$ hours less than the mean. The mode was 7 hours, slightly more than half the mean.

Fig. 2 shows the rates at which labor progressed in the four groups. It will be noted that about 65 per cent of white primiparas had labors of less than 13.04 hours (mean or average for this group) and that about the same percentage of multiparas had been delivered after less than their respective averages. These curves define the median durations of labor for the four groups as follows:

	<i>White</i>	<i>Negro</i>
Primiparas	10.59 hours	12.37 hours
Multiparas	6.21 hours	7.31 hours

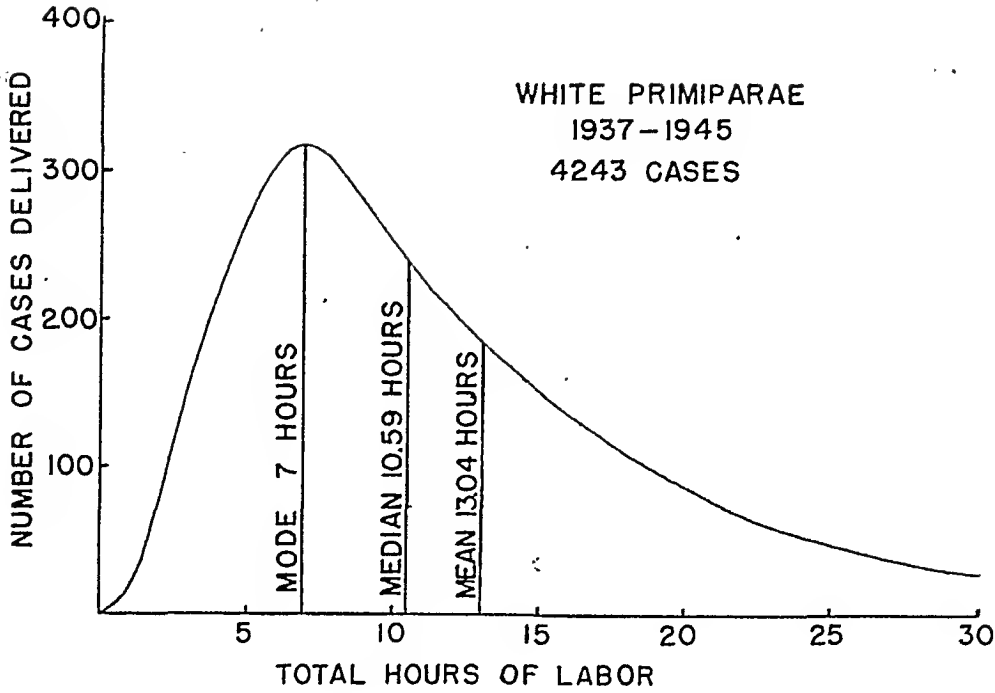


Fig. 1.

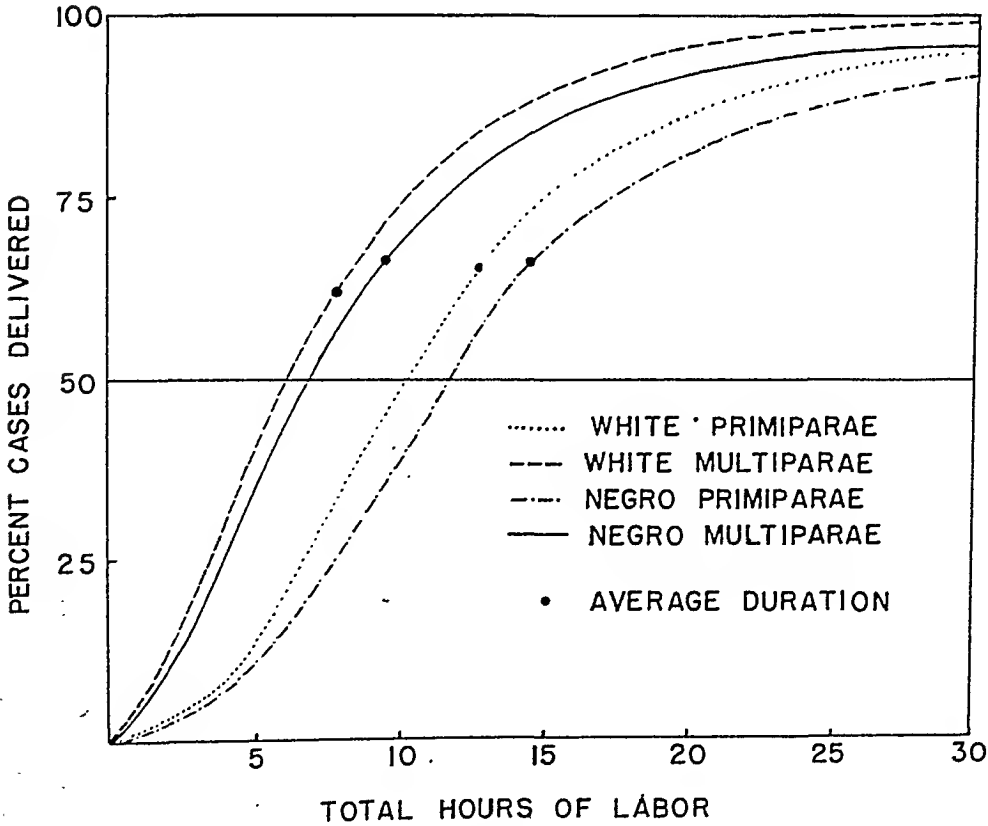


Fig. 2.

The frequency distribution curves for the four groups are shown in Fig. 3. The data on which these curves are based are given in Table II. The peaks of these curves define the modal durations of labor as follows:

	White	Negro
Primiparas	7 hours	7 hours
Multiparas	4 hours	4.5 hours

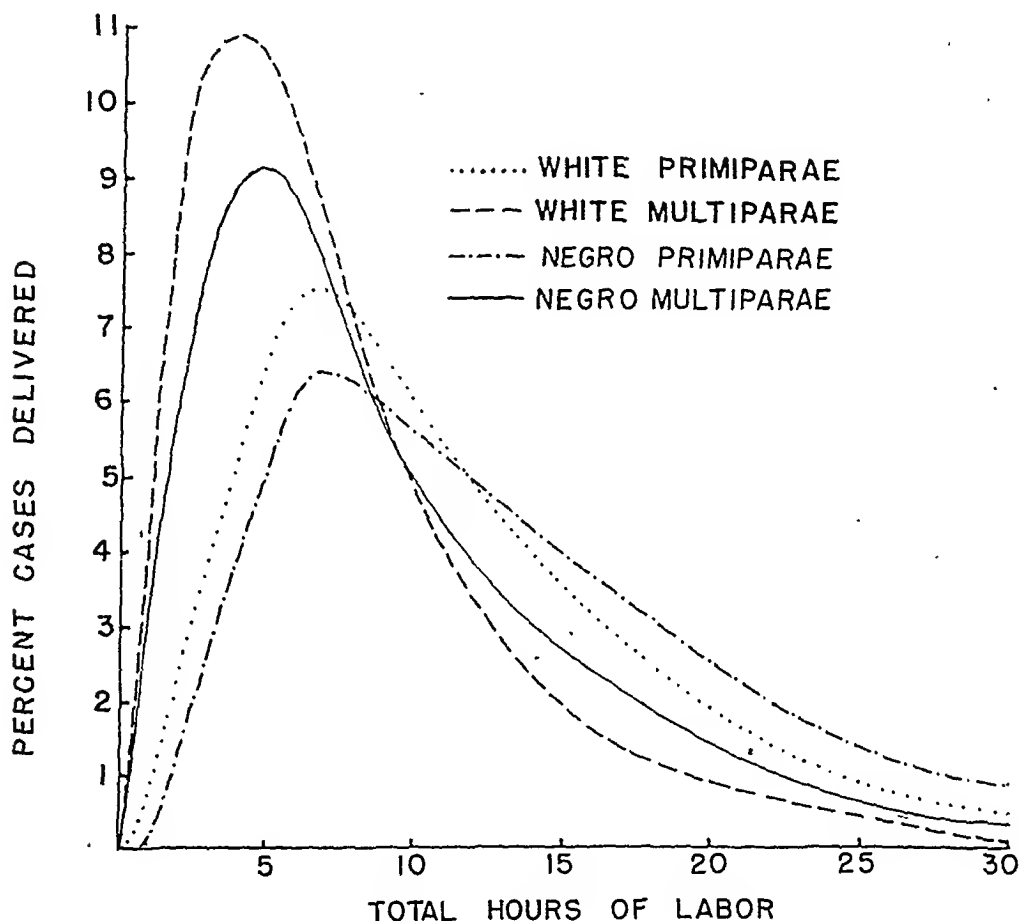


Fig. 3.

TABLE II. FREQUENCY DISTRIBUTION OF 14,775 CASES ACCORDING TO DURATION OF LABOR, RACE, AND PARITY

HOURS OF LABOR	WHITE PRIMIPARAS	WHITE MULTIPARAS	NEGRO PRIMIPARAS	NEGRO MULTIPARAS
0- 3	216	949	150	545
4- 6	735	1274	447	793
7- 9	903	824	559	560
10-12	700	493	505	318
13-15	504	236	418	227
16-18	391	169	338	199
19-21	242	96	236	111
22-24	165	64	169	83
25-27	112	47	107	57
28-30	67	20	84	29
31 and over*	208	55	265	105

*The longest labor for white primiparas was 118 hours, for white multiparas 87 hours, negro primiparas 136 hours and negro multiparas 131 hours.

It should be noted that the peaks for the Negro women do not represent as high a per cent of the total group as those for the white, but the curves are more skewed to the right. This explains the significant difference both in the mean and median durations of labor between white and negro, although the modes are essentially the same—this difference being attributable to the greater number of abnormal and prolonged labors in negroes.

With the mean, median, and modal durations of labor thus established for this series, the question arises as to which of these indices is the most descriptive and useful. If complete appreciation of a variate series is to be had, it is necessary, in the opinion of statisticians, to know the characteristics of the entire distribution, but if reliance is placed on one centering constant alone, and the material is definitely skew, the median is usually the most informative value. Applied to the duration of labor, these statements, together with the findings in the present study, indicate the desirability of laying more stress on the median duration of labor than has been done in the past. Certainly, if 65 per cent of labors terminate in less than the average time, the latter index taken alone is misleading. The main desiderata here would seem to be chiefly those figures which are most descriptive of the *typical* duration of labor in primigravidas and in multiparas, and there can be no question that the medians give a much truer picture in this regard than do the means or averages.

It is interesting, nevertheless, to compare the average values calculated in this series with the accepted values of 18 hours in primigravidas and 12 hours in multiparas, and more particularly with the averages found by Peckham in a series of 13,658 consecutive deliveries from Jan. 1, 1907 to Dec. 13, 1929 in the Johns Hopkins Hospital (Table III). These figures would tend to indicate that modern improvements in obstetrical technique and prenatal care have reduced significantly the average duration of labor. To explain fully this difference from the statistical data at hand would be impossible, but certain factors immediately come to mind which probably tend toward shortening the average duration of labor. Before 1935, the incidence of forceps deliveries in this clinic was less than 13 per cent. Recently, the popular use of elective low forceps for the delivery of primigravidas has raised this figure to 38 per cent. In the past decade, the cautious use of pituitrin stimulation in cases of uterine inertia has eliminated many very long labors from this series. These labors of exceedingly long duration would unduly increase the average duration as pointed out above. In the past few years, there has been much stress laid on the importance of diet in prenatal care. High protein diets, supplemented with vitamins and minerals, and low in salt content, may shorten the average duration of labor. These observations tend to explain to a certain degree the decrease noted in the average duration of labor as shown in Table III.

TABLE III. COMPARISON OF THE MEAN DURATION OF LABOR CALCULATED AT THE
JOHNS HOPKINS HOSPITAL

	WHITE PRIMIPARAS	WHITE MULTIPARAS	NEGRO PRIMIPARAS	NEGRO MULTIPARAS
Jan. 1, 1907 to Dec. 13, 1929 (Peckham)	16.57 hours	10.91 hours	17.66 hours	12.49 hours
Jan. 1, 1937 to Dec. 31, 1945	13.04 hours	8.15 hours	15.15 hours	10.27 hours

Conclusions

1. Previous calculations of the average duration of labor are misleading because of the incidence of prolonged labors, which distorts the frequency distribution of the cases delivered and of hours labor.

2. The median and modal durations of labor are presented as being more statistically significant than the mean or average, and certainly more in keeping with the experience of obstetricians.

3. In white primiparas, the mean was found to be 13.04 hours, the median 10.59 hours, and the mode 7 hours; in white multiparas, the mean was 8.15 hours, the median 6.21 hours, and mode 4 hours. In negro primiparas, the mean was calculated as 15.15 hours, the median 12.37 hours, and the mode 7 hours; while in negro multiparas, the corresponding findings were 10.27, 7.31, and 4.5 hours.

4. The average duration of labor is longer in negro than in white patients because of the greater incidence of prolonged labors in the former.

5. Recent improvements in obstetrical technique and prenatal care have significantly shortened the average duration of labor.

The author wishes to thank Dr. Margaret Merrell for her many helpful suggestions in the preparation of this paper.

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STUDY OF THE INCIDENCE AND OCCURRENCE OF SYMPTOMS OF VAGINAL TRICHOMONADS AND VARIOUS SPECIES OF YEAST IN PREGNANCY*

C. GORDON JOHNSON, M.D., F.A.C.S., AND RUTH MAYNE, M.S.,
NEW ORLEANS, LA.

(From the Department of Gynecology and Obstetrics, Tulane University, and
the Charity Hospital at New Orleans, La.)

A STUDY evaluating the efficacy of treatment of *Trichomonas vaginalis* vaginitis with tyrothricin suppositories¹ yielded considerable data concerning the incidence of, and symptoms caused by, vaginal trichomonads and various species of yeast. Since relatively few surveys have been published on certain aspects of the subject, it was thought that an analysis of the data might add to the general information.

The incidence of *Trichomonas vaginalis* has been reported by many workers; the average seems to be about 25 per cent.² Symptoms of pruritus and discharge are not always associated with the trichomonads. In fact, they may be absent in 47 to 87 per cent of patients with vaginal trichomoniasis.³

Yeastlike fungi were isolated from the vaginas of 32 per cent of pregnant patients and 14 per cent of gynecologic patients by Carter and Jones⁴ in 1937. Again, in 1940, Carter et al.⁵ found 33 per cent of obstetric patients had yeasts in their vaginal tracts. Carter et al.⁵ were the first to study the relationship of symptoms to genera and species of fungi. They found that in those patients who carried *Saccharomyces* or *Cryptococci* there were no symptoms referable to a mycotic infection and that only patients who carried one of three *Candida* species, *albicans*, *stellatoidea*, and *tropicalis*, had symptoms.

The purpose of this paper is to present the incidence of *Trichomonas vaginalis* and species of yeastlike fungi found in this survey and to study any association of symptoms with the two types of infection.

Materials and Methods

The patients examined were those who presented themselves to the Charity Hospital Obstetric Clinic for the first visit of their prenatal care. All were in a low economic stratum, Negro patients constituting the vast majority of those seen. Parity and the stage of pregnancy were varied.

Patients were questioned as to the occurrence of pruritus, burning on urination, and vaginal discharge. Frequently, because of reticence or indifference, no discharge was reported by the patient, but was seen on examination. No study was made for causes of symptoms other than trichomonads and yeasts.

Material from the walls of the vagina, posterior fornix, and the mouth of the cervix was collected on a sterile swab which was rubbed over the surface of a tube of Sabouraud's glucose agar before being deposited into a tube with

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one ml. sterile saline. The saline swab was examined by wet mount immediately, or within ten minutes, for *Trichomonas vaginalis*. The Sabouraud's agar was incubated at room temperature for two or three days and examined for yeast colonies. The method of Martin et al.⁶ was followed for the identification of *Candida* species; *Cryptococci* and true yeasts were not identified as to species.

Findings

Incidence of Trichomonas Vaginalis and Yeastlike Organisms.—As has been reported by Johnson et al.,¹ of 1197 pregnant women who were examined for vaginal trichomonads, 321, or 26.8 per cent, were found to harbor these organisms. A higher incidence was found in Negro women than in white (Table I).

TABLE I. INCIDENCE OF TRICHOMONAS VAGINALIS IN PREGNANCY

	WHITE	NEGRO	TOTAL
Total examined	255	942	1,197
Positive	40	281	321
% positive	15.7	29.8	26.8

Over a period of six months, March through September, 244, or 37 per cent, of 667 pregnant women were found infected with yeast or yeastlike organisms (Table II). There were 13.2 per cent more Negro women than white who carried yeast. No difference was found in the incidences during the spring and the summer months.

TABLE II. INCIDENCE OF YEAST INFECTION IN PREGNANT WOMEN OVER A PERIOD OF SIX MONTHS

	MAR. 22-JUNE 30	JULY 1-SEPT. 30	TOTAL
No. White Females			
Examined	97	72	169
Positive	26	20	46
% positive	26.7	27.7	27.2
No. Negro Females			
Examined	261	237	498
Positive	104	94	198
% positive	40.0	39.6	40.4
Total			
Examined	358	309	667
Positive	130	114	244
% positive			37.0

Table III presents the incidence of double infection found in 654 persons. As is to be expected from the above findings, the Negro group had the higher percentage of such infections.

TABLE III. INCIDENCE OF CONCURRENT YEAST AND TRICHOMONAS INFECTION IN PREGNANT FEMALES OVER A PERIOD OF SIX MONTHS

	NUMBER EXAMINED	NUMBER POSITIVE	% POSITIVE
White	169	5	2.9
Negro	485	59	12.1
Total	654	64	9.8

The number of the various species of *Candida* and the number of true and false yeasts found in this survey are shown in Table IV. Unlike the incidence

reported in North Carolina by Carter et al.⁵ and by Jones and Martin,⁷ who found the greatest number of women were infected by *C. stellatoidea* and the next highest number by *C. albicans*, the species found most often in New Orleans was *C. albicans*, and then *C. stellatoidea*. Moreover, there were fewer of the other species of *Candida* and yeasts found in this survey than in the study in North Carolina. It was also noted that a large number of these species were not quite typical in their cultural characteristics. This will be considered later.

TABLE IV. NUMBER OF VARIOUS SPECIES OF YEASTS FOUND IN 667 PREGNANT WOMEN

GENUS AND SPECIES	NO. TYPICAL	NO. ATYPICAL	TOTAL
<i>Candida albicans</i>	68	34	102
<i>Candida stellatoidea</i>	65	26	91
<i>Candida tropicalis</i>	7	1	8
<i>Candida Krusei</i>	0	1	1
<i>Candida parakrusei</i>	1	0	1
<i>Candida</i> sp. (unidentified)	3	0	3
Total <i>Candida</i>	144	62	206
<i>Cryptococci</i> sp.	37		37
True yeast	1		1
Total yeast strains			244

Incidence of Symptoms.—The association of symptoms of pruritus, burning, and discharge with vaginal trichomonads and yeasts was studied in 360 cases. Since individuals suffering from other causes of these symptoms were not excluded from the survey, the 167 women having neither of the infections in question were considered a reference group. There were 84, or 50 per cent, of these who had symptoms (Table V). Of 60 persons with trichomonads, 45, or 75 per cent, had symptoms. This finding seems significant when compared with the reference group. Of 98 persons with yeast infections, 60, or 61 per cent, had symptoms. However, this number is too close to the reference point to have any significance. It is interesting to note that 213 of the total 360 persons reported symptoms, and that of the 147 individuals having no apparent disease, 63 harbored at least one of the two types of organisms being studied.

TABLE V. INCIDENCE OF SYMPTOMS IN PERSONS EXAMINED FOR TRICHOMONADS AND YEAST

	NO. HAVING TRICH.	NO. HAVING YEAST	NO. HAVING BOTH TRICH. AND YEAST	NO. HAVING NEITHER TRICH. NOR YEAST	TOTAL
No. with symptoms	45	60	25	83	213
No. without symptoms	15	38	10	84	147
Total	60	98	35	167	360

It was thought that a study of the various species in relation to the symptoms might yield some information which was obscured by considering the yeasts as a whole. Table VI presents the number of persons, with and without symptoms, who were infected with each species. Of 48 individuals harboring *C. albicans*, 31, or 64.4 per cent, reported symptoms. Of 27 with *C. stellatoidea*, 16, or 59.2 per cent, had symptoms. It is obvious that neither of these has a significant difference in the incidence of symptoms.

TABLE VI. INCIDENCE OF SYMPTOMS IN PERSONS INFECTED WITH YEAST ONLY

SPECIES	NO. WITH SYMPTOMS	NO. WITHOUT SYMPTOMS	TOTAL
<i>C. albicans</i>	31	17	48
<i>C. stellatoidea</i>	16	11	27
<i>C. tropicalis</i>	4	1	5
<i>C. Krusei</i>	0	1	1
<i>Candida</i> sp. (unidentified)	0	1	1
<i>Cryptococci</i>	9	7	16
Total	60	38	98

As mentioned above, there were a number of species which were atypical (Table IV). The group harboring only yeast was analyzed to ascertain whether these atypical organisms occurred only in asymptomatic persons. It may be seen in Table VII that the ratio of atypical to typical strains is approximately the same in persons with pruritus and discharge as in persons without symptoms.

TABLE VII. COMPARISON OF APPEARANCE OF SYMPTOMS IN PERSONS INFECTED WITH TYPICAL AND ATYPICAL CANDIDA SPECIES

SPECIES	WITH SYMPTOMS		WITHOUT SYMPTOMS		TOTAL
	TYPICAL	ATYPICAL	TYPICAL	ATYPICAL	
<i>C. albicans</i>	20	11	11	6	48
<i>C. stellatoidea</i>	10	6	6	5	27
<i>C. tropicalis</i>	3	1	1	0	5
<i>C. Krusei</i>	0	0	0	1	1
Total	33	18	18	12	81

Using the same group of persons, the magnitude of yeastlike infection was also compared with the occurrence of symptoms. This quantitative estimation was based on the number of colonies found on the surface of the Sabouraud's slant, 50 colonies being considered the dividing line between a transitory or carrier state and true infection. Table VIII shows that of those who have less than 50 colonies, there is no difference in the number of persons with and without symptoms. However in the group having more than 50 colonies on their cultures, there are almost twice as many persons who have symptoms as those who do not. In particular is this true of the group carrying *C. albicans*. It may be concluded that the quantitative degree of infection of at least one species of *Candida* is associated with the incidence of symptoms.

TABLE VIII. COMPARISON OF APPEARANCE OF SYMPTOMS IN PERSONS WITH LIGHT AND HEAVY YEAST INFECTIONS

SPECIES	NO. OF PERSONS WITH LESS THAN 50 COLONIES		NO. OF PERSONS WITH MORE THAN 50 COLONIES		TOTAL
	WITH SYMPTOMS	WITHOUT SYMPTOMS	WITH SYMPTOMS	WITHOUT SYMPTOMS	
<i>C. albicans</i>	9	6	22	11	48
<i>C. stellatoidea</i>	5	4	11	7	27
<i>C. tropicalis</i>	0	1	4	0	5
<i>C. Krusei</i>	0	0	0	1	1
<i>C. sp.</i>	0	0	0	1	1
<i>Cryptococci</i>	3	3	6	4	16
Total	17	14	43	24	98

In the method used for identifying *Candida* species, only one colony is picked from the Sabouraud's slant. This means that if two species are present, one is missed. In a small series of persons who came to the clinic regularly for

other treatment, cultures were taken over a period of one to eight weeks. In two of 20 persons thus examined, two species were recovered at different times. In five persons, unidentified species which closely resembled the persistent, typical culture of each, were found. Thus, there is a definite chance that two or more *Candida* species can be carried simultaneously, and that the second is missed when only one colony is picked for identification.

Comment

The incidence of *Trichomonas vaginalis* found in this survey is much the same as that found in other parts of the country. The higher incidence in Negro persons than in white does not indicate racial predilection but only emphasizes that spread of infection is aided by crowded living conditions and the general lack of personal cleanliness prevalent in the underprivileged.

The incidence of vaginal mycosis was approximately the same as that found by Carter et al.^{4, 5} and by Martin et al.⁶ in Durham, North Carolina, ours being only slightly higher.

It was noted during the war that all types of fungi abound in the tropical countries. There was no opportunity in this survey to compare vaginal mycotic incidence with temperature or humidity, since the weather conditions in New Orleans were approximately the same in the spring and summer months. The average temperature for the spring was 75.9 degrees F. and that for summer 81.6 degrees F., with a maximum difference of 10 degrees between the averages of the six months. Likewise there was a maximum difference of only 11 per cent between the average relative humidity of each of the six months. The average humidity of New Orleans and that of Durham are also only slightly different. Thus theories of a correlation between the incidence of vaginal mycoses and humidity and temperature cannot be proved by these data. However, there is at least a negative value here, in that the findings are in accord with such theories.

No explanation can be offered for the different relative incidence of *C. albicans* and *C. stellatoidea* in the two cities. It is more than probable that these differences are quite within the realm of chance.

In studying association of symptoms with the two diseases, it was necessary to compare the infected groups with the uninfected group. The reason for this was that due to the large size of the clinic, no routine examination was made for other infections causing the same symptoms. It was found that 50 per cent of women uninfected with vaginal trichomonads or yeasts have symptoms of pruritus or discharge. Therefore it was expected that 50 per cent of the infected persons might also have symptoms which were not caused by their specific infection. An increase of 25 per cent in the incidence of symptoms therefore seems significant and implies that the trichomonads are associated with symptoms. It has been proved by Trussel and Plass⁸ that *Trichomonas vaginalis* can cause such symptoms. However, an increase of only ten per cent, as in the case of yeast infection, cannot indicate an association of the infection with symptoms.

In the same manner, an analysis was made of the data concerning symptoms in persons with the various species of *Candida* (Table V). However, increases over the base line of 14.4 and 9.2 per cent, for *C. albicans* and *C. stellatoidea*, respectively, cannot be interpreted as being significant. There were too few persons in the group having *C. tropicalis* to make any comments other than to point out that all but one person had symptoms. The group harboring Cryptococci had almost the same number having symptoms as those that did not. It may be seen that these data take the direction of agreement with the work of Carter⁵; that is, *C. albicans*, *C. stellatoidea*, and *C. tropicalis* are associated with symptoms while the other yeasts are not.

There was a possibility that strains of *Candida* which were atypical might be considered rough, and like the rough Pneumococci, be avirulent. However, no such correlation could be made (Table VI). According to these data, atypical cultural characteristics of the *Candida* species do not imply change in virulence.

There was definite correlation of magnitude of infection with symptoms. It is possible that a carrier state may exist for a time and then change to a state of disease with symptoms. This change would probably be dependent upon changes in the condition of the host. Or it is possible that the patients with fewer numbers of organisms were examined at the beginning of the infection and that symptoms would appear when the number of organisms increased. It would be of interest to take numerous cultures of a few such persons over a period of time to study these two theories.

Since there is a possibility that the patient can carry two different species of yeasts, such a project as suggested above would be very desirable. It would eliminate some of the errors occurring in surveys made from single examination and single colony identification.

Summary and Conclusions

1. *Trichomonas vaginalis* was found in 321, or 26.8 per cent, of 1197 pregnant women who were examined by the wet mount method.

2. Cultures of yeast or yeastlike organisms were obtained from the vaginas of 244, or 37 per cent, of 667 pregnant women.

3. Both trichomonads and yeast were found in 64, or 9.8 per cent, of 654 pregnant women.

4. More Negro women than white harbored the two infections. This fact was undoubtedly not due to racial predilection but to differences in mode of living and personal hygiene.

5. *Candida albicans* and *C. stellatoidea* comprised the majority of strains of yeasts found in this survey, *C. albicans* being the greatest in number.

6. Although symptoms of discharge, burning, and pruritus can be caused by both *T. vaginalis* and certain species of yeasts, their mere presence does not indicate coincidence of symptoms.

7. No definite relationship of symptoms with any species of yeast was found. However, the data pointed in the direction of agreement with Carter, that *C. albicans*, *C. stellatoidea*, and *C. tropicalis* are associated with symptoms while the Cryptococci are not associated with pruritus and discharge.

8. No relationship of atypical strains of *Candida* with the asymptomatic state was found.

9. The quantitative degree of infection with yeasts, particularly *C. albicans*, was discovered to be connected with the appearance of symptoms of pruritus and discharge.

10. The method of collecting yeast samples, using only one examination of the patient and picking only one colony for identification, is reliable within limits as a basis for studying incidence. Definite conclusions may be drawn from such a survey when the numbers are large; however, the chance of missing a concurrent infection with another species of yeast might cause erroneous deductions when the numbers are small.

11. A study should be made to determine whether those persons having no symptoms and harboring a few organisms are in a carrier state or in one of incipient infection.

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A STUDY OF THE USE OF PENICILLIN IN PREMATURE RUPTURE OF THE MEMBRANES

JOHN H. E. WOLTZ, M.D., CHARLOTTE, N. C., AND THEO. S. STASHAK, M.D.,
PHILADELPHIA, PA.

*(From the Department of Obstetrics and Gynecology, School of Medicine,
University of Pennsylvania)*

IT HAS been shown that penicillin reaches the human amniotic fluid and fetal tissues when administered to the mother. As a result, it has been suggested that it might be employed as a protection against intrauterine infection following premature rupture of the amniotic membranes.¹⁻⁴

The present investigation was undertaken in order to determine specifically the effect of penicillin upon (1) the bacterial content of the cervix at delivery, (2) the latent period between the rupture of the membranes and the onset of labor, (3) maternal morbidity, and (4) fetal mortality.

Methods and Material

The study was made from approximately one thousand consecutive admissions to the Obstetric Service of the Hospital of the University of Pennsylvania. Those qualifying were patients whose membranes had ruptured at home, and whose uterine contractions had not started prior to admission to the hospital. In each case, rupture of the "bag of waters" was confirmed by a positive "dye" (bromthymol blue) test.⁵ There were no cases of prolapse of the cord. All patients fell into labor spontaneously; none were examined vaginally. All women were confined to bed on admission to the hospital; alternate ones received 12,500 units of penicillin* intramuscularly every three hours from the time of admission until delivery. Oral temperatures were recorded every four hours day and night.

Fifty-seven patients were studied; 29 received penicillin and 28 received none. In no case was it necessary to abandon the study in the interest of the patient. One woman in each group stopped leaking fluid, did not go into labor, and was discharged from the hospital.

At delivery, cervical cultures were taken from 24 of the 29 patients receiving penicillin and from 21 of the 28 women who received none.

Table I shows the frequency with which various bacteria were observed in the 57 patients. Pathogens were present in the cervixes of both treated and control patients; gonococci were present in one of the untreated patients. Only two (6.9 per cent) of the patients receiving penicillin became morbid,† whereas six (21.4 per cent) of the control group did so.

*The penicillin sodium was furnished through the courtesy of the Department of Medical Research, Winthrop Chemical Company.

†Any patient with a temperature rise to 100.4 degrees F. on any two days, exclusive of the first 24 hours post partum, was considered morbid.

TABLE I. BACTERIA PRESENT IN THE CERVICES OF ALL PATIENTS
AT THE TIME OF DELIVERY

ORGANISMS	PATIENTS	
	29 TREATED	28 CONTROL
<i>Staphylococcus albus</i>	6	13
<i>Staphylococcus aureus</i>	1	1
<i>Staphylococcus hemolyticus</i>	2	2
<i>Micrococcus flavus</i>	1	1
Diphtheroid bacillus	11	5
<i>Bacillus lactis aerogenes</i>	3	-
<i>Bacillus proteus</i>	3	-
<i>Bacillus coli communis</i>	18	4
Yeast cells and bacilli	1	-
<i>Streptococcus pyogenes hemolyticus</i>	1	1
<i>Streptococcus viridans</i> unidentified	1	3
<i>Streptococcus nonhemolyticus</i>	7	11
<i>Streptococcus</i> morphology (unidentified)	1	1
<i>Hemophilus</i>	5	5
<i>Gonococcus</i>	-	1
No growth	2	2

The morbid patients (Table II) showed a variety of bacteria. Penicillin-sensitive and penicillin-resistant organisms were cultured from the cervixes of both the treated and untreated women.

TABLE II. BACTERIA PRESENT IN THE CERVICES OF MORBID PATIENTS
AT THE TIME OF DELIVERY

ORGANISMS	MORBID PATIENTS	
	2 TREATED	6 CONTROLS
<i>Staphylococcus albus</i>	2	3
<i>Staphylococcus aureus</i>	1	1
Diphtheroid bacillus	2	3
<i>Bacillus coli communis</i>	2	3
Yeast cells and bacilli	1	-
<i>Streptococcus pyogenes hemolyticus</i>	-	1
<i>Streptococcus viridans</i> unidentified	1	-
<i>Streptococcus nonhemolyticus</i>	1	4
<i>Hemophilus</i>	2	3
<i>Gonococcus</i>	-	1
Total different organisms cultured from cervix	12	19

The number of hours between the rupture of the membranes and the onset of labor is shown in Table III.

The thirty-sixth week of gestation is taken as a dividing line between the term and premature gestations.

In general, the latent periods were not affected by penicillin in either the term or premature gestations. This suggests that penicillin has little if any oxytocic effect on the uterus at or near term. The average latent period was approximately 23 per cent longer in the case of the pregnancies which terminated prematurely than in the case of the patients who went to term.

The effect of the latent period on morbidity is indicated in Table IV. There was no definite relationship between the length of the latent period and the frequency of maternal morbidity. It will be noted, however, that all morbidities occurred in patients whose latent periods exceeded twenty hours.

TABLE III. TIME INTERVAL BETWEEN RUPTURE OF THE MEMBRANES AND ONSET OF LABOR

INTERVAL (HOURS)	GESTATION OF PATIENTS			
	NO. TREATED		NO. CONTROLS	
	UNDER 36 WEEKS	OVER 36 WEEKS	UNDER 36 WEEKS	OVER 36 WEEKS
1-10	-	3	-	1
11-20	2	4	-	4
21-30	1	4	1	4
31-40	2	2	1	3
41-50	1	2	1	1
51-60	-	2	1	-
61-70	-	-	-	3
71-80	-	-	-	-
81-90	1	-	-	1
91-100	1	2	2	1
131-140	-	-	-	2
191-200	1*	-	-	-
240	-	-	1*	-
Total patients	9	19	7	20
Average latent period (hours)	43.7	33.4	58.3	43.0

*Omitted in average.

TABLE IV. MORBIDITY IN RELATION TO DURATION OF INTERVAL BETWEEN RUPTURE OF MEMBRANES AND DELIVERY

INTERVAL (HOURS)	PATIENTS			
	NO. TREATED		NO. CONTROLS	
	MORBID	NONMORBID	MORBID	NONMORBID
1-10	-	3	-	1
11-20	-	6	-	4
21-30	1	4	3	2
31-40	-	4	1	3
41-50	1	2	-	2
51-60	-	2	1	-
61-70	-	-	-	3
71-80	-	-	-	-
81-90	-	1	-	1
91-100	-	3	-	3
101-110	-	-	-	-
131-140	-	-	1	1
191-200	-	1*	-	-
231-240	-	-	-	1*
Total patients	2	26	6	21
Average latent period (hours)	35	36.6	50	50.5

*Not included in the average.

There were three infant deaths (Table V). Two of the fetuses died in utero. The mother (A.C.) of one of these received penicillin. This fetus was found to have a negative culture from its heart blood. Postmortem examination showed congenital heart disease and evidence of possible erythroblastosis fetalis. The mother (D. F.) of the second infant who died in utero received no penicillin. A blood culture from this infant's heart was positive for hemolytic staphylococcus albus. The cause of its death was believed to be due to septicemia.

The third infant died of pneumonia, which disease was confirmed at post-mortem. Difficulty of delivery and a prolonged apnea were considered contributory causes of this death. The mother had received penicillin.

TABLE V. INFANT DEATHS

PATIENT	PENICILLIN	GESTATION WEEKS	LATENT PERIOD HOURS	MORBID	INFANT				POST MORTEM
					DEATH	WT. GRAMS	CAUSE	CULTURE HEART BL.	
A. C. No. 23224	Yes	32	196	No	Intrauterine	1670	Congenital heart dis- ease—erythro- blastosis	No growth	Congenital heart dis- ease, erythro- blastosis
D. F. No. 23368½	No	34	36	No	Intrauterine	2190	Septicemia	Hem. staph. albus	Negative (cause un- determined)
R. S. No. 24777	Yes	40	52	No	Neonatal	3640	Prolonged labor, high midforceps, apnea	Not taken	Pneumonia

Summary

A study of the use of penicillin in premature rupture of the membranes is presented. The effects of penicillin on the bacteriology of the cervix, the latent period between the rupture of the membranes and the onset of labor, maternal morbidity, and fetal mortality are shown.

Conclusions

Penicillin administered to patients with premature rupture of the membranes has little, if any, effect upon the bacteria cultured from the cervix at or near term.

It has little, if any, oxytocic effect on the term or near-term uterus.

Premature rupture of the membranes of less than twenty hours' duration was not followed by maternal morbidity. Beyond that length of time there is no definite relationship between duration of premature ruptured membranes and maternal morbidity.

Administration of penicillin to patients with premature rupture of the membranes influences favorably the frequency of maternal morbidity. Therefore its routine use under such circumstances is indicated.

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SPLENECTOMY IN PREGNANCY: ITS HEMATOLOGIC INDICATIONS AND OBSTETRIC MANAGEMENT

ALLAN C. BARNES, M.S., M.D., AND CHARLES A. DOAN, M.D.,
COLUMBUS, OHIO

(From the Department of Obstetrics and Gynecology and the Hematology Clinic, the Ohio State University Medical School)

THE necessity for splenectomy during pregnancy in the therapy of certain hematologic dyscrasias is relatively rare, and surgery under such circumstances is still a questioned procedure. The present discussion of the problem is based on three splenectomies performed on pregnant women for critical hematologic indications. While this is a small group, we know of no similar consecutive series. During the past seventeen years special emphasis has been placed upon the role of the spleen in human disease in the Hematology Clinic at this University. From a large clinical experience in a wide variety of hematologic dyscrasias, some 210 therapeutic splenectomies have been recommended and accomplished.^{1, 2} The three pregnant women in this series who presented aggravated hypersplenic syndromes are here considered from the obstetric point of view.

Splenectomy for blood dyscrasias complicating pregnancy has been reported ten times. In four of these cases the indication was Banti's syndrome, and in six thrombocytopenic purpura. An additional, unreported case operated upon for congenital hemolytic icterus has come to our attention,³ and undoubtedly other cases exist which have not been recorded.

Hesseltine in 1930⁴ and McKenzie in 1936⁵ each reported a splenectomy performed for Banti's disease during pregnancy. The outcome in each case was successful. In 1937, Serbin⁶ reported two patients operated upon following this diagnosis. Finn in 1944⁷ collected from the literature four cases of splenectomy for thrombocytopenic purpura in pregnancy. These had been reported by Berstein, Newman and Hitzig (1939), Phythyon and Lartz (1943), Polowe (1944) and Gromen's reference to a splenectomy in pregnancy for thrombocytopenic purpura performed by Garlock (date not given). In 1946, Nordland, Ylvisaker, Larson, and Reiff⁸ added a case, as did Dinsmore and Dutlinger.⁹

Case Reports

CASE 1.—V. M., a 21-year-old white woman was admitted to the hospital with a chief complaint of bruises and purpuric spots on the legs and abdomen, and fatigability. She was a gravida i, seven months pregnant at the time, and had been under the care of her physician since the third month. There had been no vaginal bleeding, but vitamin K had been administered without benefit for the purpuric areas on the legs and for irregular bleeding of the gums which the patient had suffered.

Physical examination revealed evidences of recent bleeding of the gums, multiple purpuric spots over the legs and abdomen, and numerous petechiae of the mucous membranes. The fundus of the uterus was just above the umbilicus and the fetal heart sounds were of good quality. Pelvic measurements were normal and the remainder of the physical examination was not remarkable.

Preoperatively the patient's platelet count ranged between 6,000 and 12,000 (normal for the method used, 750,000+ per c.mm.). White cell count, differential, red count, and hemoglobin were all normal for the duration of gestation. Bone marrow studies showed abundant young and mature megakaryocytes, a normal quantitative differential with a shift to the left of both red and white elements consistent with the patient's pregnancy. Prothrombin and vitamin C deficits were ruled out. The diagnosis of essential thrombocytopenic purpura was made and the patient was prepared for splenectomy. Whole blood transfusions of 500 c.c. were given the day before and the day of surgery; 10 mg. of Proluton were administered daily from the day before operation throughout the patient's hospital stay.

Operation was carried out under cyclopropane and ether anesthesia. The spleen was relatively posterior and had a moderately short pedicle. The spleen was removed and extensive exploration carried out for accessory spleens. None were located, the wound was closed, and the patient returned to her bed in good condition. The postoperative course was complicated only by a small wound hematoma which did not become infected and which was drained on the tenth day. The platelet count improved slowly but steadily following the splenectomy. Postoperatively on the day of operation, the platelets rose to a high of 39,600; during the next three days to 48,020, 61,600 and 70,560 respectively. By the fifth postoperative day the platelet count had risen to 306,000 and the following day it was 497,700 per c.mm. Throughout the remainder of the patient's stay in the hospital the circulating thrombocytes ranged between 400,000 and 800,000 per c.mm. with complete cessation of all clinical manifestations of purpura.

At the conclusion of the operation the fetal heart rate was 160. Two hours later it had returned to 130, and remained normal throughout the hospital course. There were no painful uterine contractions and no vaginal bleeding. The Proluton was discontinued upon discharge from the hospital, and the remainder of the patient's antepartum course was uneventful. Two months postoperatively she went into labor spontaneously and delivered a normal term viable fetus with no difficulty, and without excessive blood loss. No blood counts are available on the infant, but it was without purpuric symptoms and has manifested no hemorrhagic tendencies. The subsequent, nonobstetric course of this patient has been reported elsewhere.¹⁰

CASE 2.—M. J. H., aged 23 years, a primigravida four months pregnant, was admitted with the chief complaints of intermittent jaundice, extreme exhaustion, and exertional dyspnea. The family history revealed that the patient's father had had congenital hemolytic icterus, and probably her paternal grandfather also. Two brothers had histories of intermittent attacks of jaundice. The patient's own previous attacks had been chiefly related to exhaustion and fatigue, but during this pregnancy there had been an associated definite icterus. During a routine antepartum checkup, her physician discovered that the hemoglobin and red count were falling abnormally and referred her to the hospital at once for further studies.

Examination on admittance revealed no icterus, marked pallor of the skin and mucous membranes, no petechiae. The spleen was palpable below the costal margin and tender. The uterine enlargement was proportionate to the patient's pregnancy. The red count was 2,250,000, hemoglobin 9.5 Gm., white count was

11,000 with a normal distribution. The reticulocyte level ranged between 16 and 23 per cent. Red cell fragility started at 0.550 and was complete at 0.267 (normal for this method 0.412 to 0.300). Urinalysis was negative; icteric index 15; van den Bergh was direct negative, indirect, 1.62. A diagnosis of congenital hemolytic icterus, subacute activity, was made and the patient prepared for splenectomy.

Proluton, 10 mg. a day, was started and continued until the patient was discharged from the hospital. Cyclopropane anesthesia was employed and the spleen removed without difficulty. Exploration failed to reveal accessory spleens, and no abnormality of the gallbladder, bile ducts, or liver was noted. Post-operatively the patient received 1,000 c.c. of washed cells. Erythrocyte destruction ceased immediately, and the red cells rose slowly to 3,200,000 per c.mm. Convalescence was uneventful. The patient was discharged on her twelfth post-operative day, there having been no evidence of abnormal uterine activity in the meantime. The patient continued on to term, went into labor spontaneously, and delivered with outlet forceps after fourteen hours. The baby had a normal neonatal course without evidence of icterus. Blood count on the third day of life revealed 14,300 leucocytes with a normal differential; an erythrocyte count of 4,930,000 per c.mm., with a reticulocyte level of 5.6 per cent. The hemoglobin was 20.4 Gm. and the platelet level 1,397,120. The baby was discharged with the mother on the tenth day, having regained birth weight. At the age of 6 months a hematologic checkup was obtained on the baby which revealed no pathology. The reticulocyte level at that time was 0.8 per cent and the red cell fragility was within normal limits.

CASE 3.—H. B., a 31-year-old primigravida entered the hospital when five months pregnant with the complaints of purpuric spots over legs and abdomen and of epistaxis. The duration of her hemorrhagic manifestations and of her pregnancy were identical, the first bleeding from the nose having followed her last menstrual period. The patient also had had moderately severe nausea and vomiting the first four months, which were beginning to subside at the time of hospital admittance.

Physical examination revealed a well-developed and well-nourished white woman with multiple petechiae over skin and mucous membranes. The uterus was 22 cm. above the symphysis, fetal motion and heart sound identifiable. Pelvic measurements were normal.

There was no familial history of purpura, and, although the patient had worked as a welder until two months prior to the onset of her bleeding tendencies, the history suggested the pregnancy as the most probable precipitating mechanism. This was supported by the bone marrow findings, which failed to reveal any evidence of toxic damage to the normal elements. The platelet count ranged between 21,000 and 47,000, the marrow revealed megakaryocytosis, the remainder of the blood picture being compatible with the pregnancy. The basal metabolic rate was minus 11 and the prothrombin level 115 per cent. The hematologic diagnosis was essential splenic thrombocytopenic purpura, and the patient was prepared for splenectomy.

A program of thyroid and Proluton was started preoperatively, and 500 c.c. of fresh blood were given prior to surgery. Under cyclopropane anesthesia the spleen was exposed, found to be moderately enlarged, and removed without difficulty. An accessory spleen was found at the hilus. Gentle exploration revealed no other intra-abdominal abnormalities and the wound was closed with only moderate oozing.

The surgical and obstetric convalescence was uneventful. There were no uterine cramps, and no vaginal bleeding. The patient was allowed out of bed

on the third postoperative day and was discharged the twelfth day. The platelet response was satisfactory. By the evening of the day of surgery the count had risen to 60,000 and the following morning it was 311,300. It remained over 300,000 for the next five days and between 100,000 and 200,000 for the duration of the patient's hospitalization.

The patient continued under direct antepartum observation. Her course was uneventful, and her platelet count ranged between 200,000 and 350,000 at each visit. She was admitted at term in active labor and had a short (seven hour), relatively easy primiparous labor concluded with outlet forceps and left mediolateral episiotomy. Blood loss was small, and the postpartum course uneventful. The episiotomy healed by primary intent. Blood counts on both the mother and baby at the time of delivery and later showed no abnormality. The baby was weaned and was discharged with a gain over birth weight.

Discussion

It cannot be stressed too frequently that the pregnant patient demonstrating hemorrhagic tendencies should have the benefit of a complete hematologic investigation. The symptomatic administration of vitamin K to the first of these three patients without proper study succeeded only in delaying specific treatment. Complete evaluation of the peripheral blood, sternal marrow aspiration with supravital studies, the adrenalin test for splenic contraction, and the biopsy this provides of the cells sequestered by the spleen all contribute essential data. In the hemorrhagic states hypoprothrombinemia and hypovitaminosis C must be ruled out, as well as allergic or amyelophthisic thrombocytopenias.

In the gravid patient who has had such studies and whose diagnosis is firmly established, however, we do not feel that the presence of the pregnancy alters the hematologic indications for splenectomy. The two diagnoses represented by the cases here reported—congenital hemolytic icterus and thrombocytopenic purpura hemorrhagica—are the most frequently met indications. Primary splenic neutropenia and panhematopenia¹¹ may also be met in the pregnant patient.

Wolff and Limarzi¹² have recently stated that in thrombocytopenic purpura "splenectomy is best done following the pregnancy and during a remission of the disease, but may be performed if the patient is seen during the first trimester." They feel that this represents "a conservative attitude toward the pregnancy." With this dictum, as well as its reasoning, the present writers disagree. In our opinion, the hemorrhagic state represents a greater hazard than does the operation of splenectomy irrespective of the trimester of the pregnancy, and true conservatism indicates a correction of the hematologic disorder as soon as the diagnosis is established and the patient properly prepared.

While purpuric states may not influence postpartum blood loss,^{7, 13} antepartum and intrapartum hemorrhage remains a constant threat, and intrauterine fetal death from retroplacental hemorrhage has been reported.⁶ On the other hand, splenectomy, even with thorough search for accessory spleens, should not precipitate labor. While each of these patients was on an "antiabortion regime" of corpus luteum products, thyroid, and adequate sedation, it remains our conviction that gentleness of intra-abdominal manipulation at the time of surgery

constitutes the most important single measure to prevent the onset of uterine contractions.

The relationship between the pregnancy and the hematologic status is of interest. Where the two conditions are closely related by history (Case 3) the pregnancy may be considered the precipitating factor.¹⁴ It is not, however, the causative factor, the cause remaining splenic sequestration and destruction. Insofar as the baby is concerned, the hereditary nature of the hemolytic icterus is well known. With respect to thrombocytopenic purpura, we feel, as previously expressed by Wiseman, Doan and Wilson,¹⁵ that the condition may be congenital, but that it has not yet been established as hereditary.

Summary

Three cases of splenectomy performed during pregnancy are presented. Two of these were for thrombocytopenic purpura and one for congenital hemolytic icterus. In each case the pregnancy proceeded to term and a normal child was delivered. The place of splenectomy in the treatment of hematologic disorders occurring during pregnancy is discussed.

The authors wish to express their appreciation to Dr. B. K. Wiseman for permission to report on two of his private patients. Dr. G. M. Curtis performed the splenectomies and Dr. Charles Pavey delivered one of the patients.

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ARRHENOBLASTOMA OF THE OVARY*

KANE ZELLE, B.S., M.D., CHICAGO, ILL.

(From the Department of Gynecology and the Henry Baird Favill Laboratory of St. Luke's Hospital, and the Department of Obstetrics and Gynecology of Northwestern University Medical School.)

NINETY-FOUR cases of arrhenoblastoma of the ovary have been reported in the literature. No single theory of the pathogenesis of these tumors has been universally accepted. The two theories most widely supported at this time are those advanced by Meyer,¹ who suggested that arrhenoblastomas arise from latent male elements in the ovary, and the teratomatous theory first suggested by Popoff.² The report of another case seems justified because of the debatable pathogenesis of these tumors, and because of the interesting problems which arise in conjunction with the multiplicity of tissues found on pathologic examination. Endocrine interrelationships and the mode of action of these hormone-producing tumors are also debatable.

Dr. D. D. Odell of Bryan, Ohio, has very kindly furnished the entire tumor for study, and has supplied the following history, physical examination, and follow-up. Dr. Edwin F. Hirsch and Dr. John L. Brewer have given invaluable aid in the study of these tissues.

The patient, Mrs. V. C., aged 23 years, white, married, gravida i, entered the Cameron Hospital, Bryan, Ohio, on the service of Dr. D. D. Odell. Two years prior to hospital admission, the patient had a normal spontaneous delivery of a full-term pregnancy. Following delivery there was a resumption of her normal menstrual cycle, and then her periods became more frequent, occurring at two-week intervals, and finally progressing to almost continuous spotting. One year prior to admission she became completely amenorrheic, and at the same time first noticed that her voice was becoming appreciably deeper. Six months before operation a marked growth of hair developed on the patient's upper lip and about her breasts. There was a noticeable enlargement of the lower abdomen, and the patient believed herself to be pregnant.

Physical examination revealed a well-developed and well-nourished white woman, 23 years of age. She did not appear to be acutely ill. Her voice was a rich baritone, and there was a definite growth of hair on the upper lip and chest. Pelvic examination revealed a freely movable, somewhat cystic, smooth, round mass that extended to the umbilicus. The mass seemed to be more prominent on the left side. The uterus was of normal size and was palpated separately from the mass. A preoperative diagnosis of arrhenoblastoma of the ovary was made.

On Sept. 26, 1945, under general anesthesia, an abdominal section was performed by Dr. D. D. Odell. There was a multiloculated cystic and solid left ovarian tumor. The right ovary and tube were normal. Exploration of both suprarenal regions and of the abdomen revealed no tumor or metastases. A left salpingo-oophorectomy was done.

*Presented before the Chicago Gynecological Society, March 22, 1946.

Pathologic Examination.—The tumor had solid and multiloculated cystic tissues and weighed 14 pounds. It was blue-gray and the intact capsule was smooth. On many surfaces made by cutting there were multiple smooth cysts ranging from a few millimeters to six centimeters in diameter. In the lumens of some of the cysts was a mucoid substance. The cystic structures were separated by fibrous septums. About 40 per cent of the tumor was solid, and these portions were well demarcated, firm, and tan-brown in color. There were numerous large regions of hemorrhage and necrosis.

Microscopic examination was made of multiple sections cut from sixty-five blocks taken from representative regions of the tumor. The tissues were fixed in formalin and stained with hematoxylin-eosin, Mayer's mucicarmine, Laidlaw's silver stain, phosphotungstic acid and Foote's modification of Masson's trichrome stain. Sections were also stained after the method of Bennett² with phenylhydrazine to demonstrate 17-ketosteroids. Fat stains were made of frozen sections from many regions. A scant ovarian stroma along the periphery was normal, but there were no primordial or developing follicles. In one section a structure was observed which may have been an atretic follicle, but this was not positively identified. There were many corpora albicantia. The solid portions were tumor tissues with a wide range in morphologic structures. The tumor cells, in a background of edematous reticular stroma, were generally of two types. In regions in which the stroma predominated there were spindle-shaped cells with scant cytoplasm and oval vesicular nuclei. In some places these cells were arranged in parallel rows forming retelike structures. (Fig. 1.) The second predominant type of tumor cell was polygonal, medium in size, with oval or round coarsely granular nuclei and a moderate amount of neutrophilic cytoplasm. Mitotic figures were rare. The polygonal cells were in groups, or islands, and arranged in sheets, cords, strands, or whorls in most regions, but in others they appeared as mosaics lying in tissue crevices and with bizarre lumenlike structures. Throughout the tumor were foci of edema, and in these the appearance of the cells was considerably altered. The lobules of edematous cellular tissue were subdivided by fibrous connective tissue septums which surrounded small groups of tumor cells. The tumor cells themselves had signs of degeneration, with pyknotic nuclei, vacuolated cytoplasm, and in some instances disintegration of the cell membrane. (Fig. 2.) These regions of edema appear similar to published photomicrographs of adrenal-like ovarian tumors. There were also transition stages from the tumor cells which showed no degeneration to the vacuolated degenerating cells lying in the foci of edema described above. In the transition zones, single cells or small aggregates with pyknotic nuclei and vacuolated cytoplasm were seen in the midst of a large number of normal tumor cells. Retrogressive changes seemed to be most marked in the large cells. Multinucleated forms were seen in some regions.

Wherever loose connective tissue was found there were cells which resembled the interstitial cells of the testes. (Fig. 3.) These cells occurred singly and in groups. Their nuclei were round, though occasionally irregular, and the nuclear membrane was prominent. The nucleolus was usually eccentric. In Sudan-stained sections the interstitial cells and the polygonal tumor cells were laden with lipid droplets. The cystic structures described grossly were lined by low cuboidal or keratinized epithelium.

In some sections were small foci of gland structures lined by tall columnar epithelium. (Fig. 4.) These nonciliated epithelial cells had oval nuclei arranged regularly at the base of the cells. They contained no silver-reducing granules. Interspersed throughout the columnar epithelium of the glands were goblet cells. In the lumina of the glands was a homogenous mucoid substance. The goblet cells and the substance in the lumen of the glands stained darkly with Mayer's mucicarmine stain.

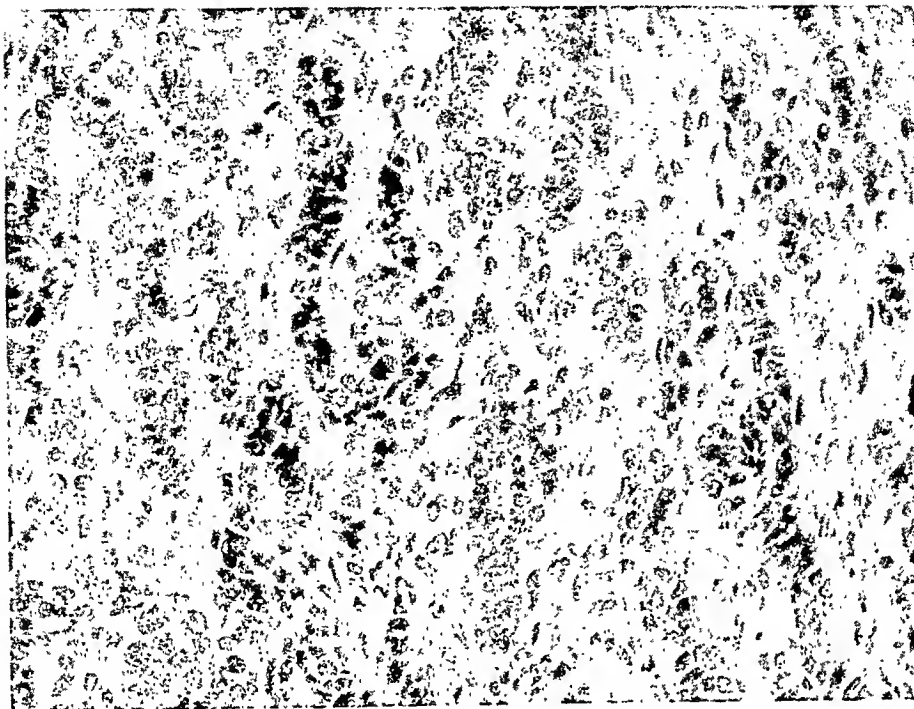


Fig. 1.—Tumor cells forming reticulate structures are present in many sections.

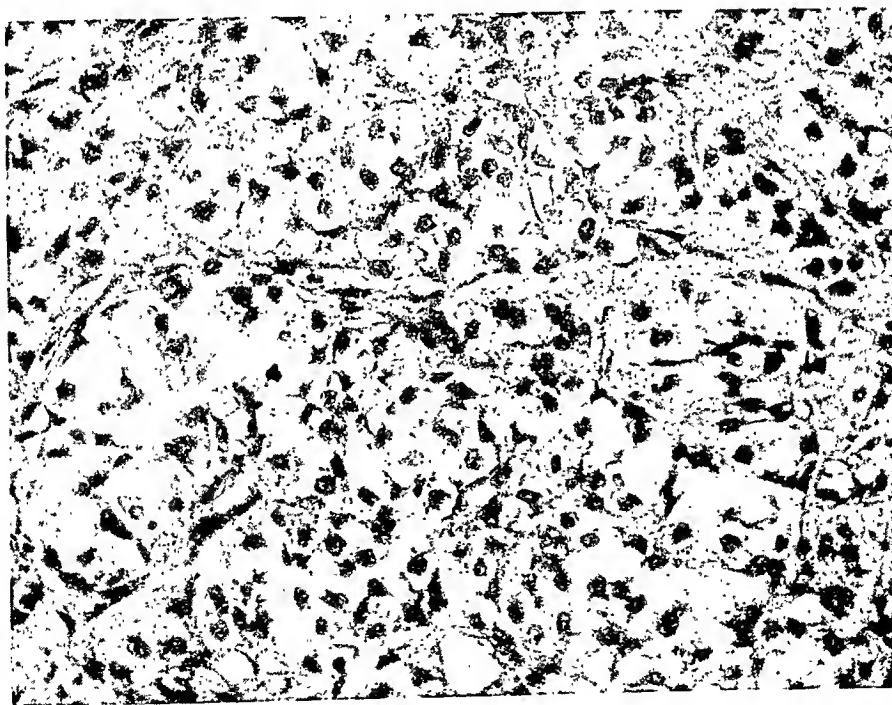


Fig. 2.—Some of the tumor cells in regions of edema have vacuolated cytoplasm, pyknotic nuclei, and dissolution of the cell membrane, indicative of degeneration.

The tumor had a reticular stroma, varying from coarse to fine fibers in character, and was widely infiltrated with plasma cells and lymphocytes. There were many small blood vessels whose lumina were filled with red blood cells.

The sections stained with phenylhydrazine had a marked yellow color, as did adrenal tissues stained by similar solutions at the same time. Neutral tissues (heart, spleen, thyroid) stained simultaneously as controls did not become yellow.

Examination of the patient eighteen months after removal of the tumor showed an almost complete regression of the hirsutism. Menstruation began four months after excision of the tumor, and her menstrual cycles have remained normal. Pelvic examination revealed no abnormalities. Her general health is excellent.

In classifying arrhenoblastomas, most authors follow the grouping proposed by Meyer,¹ who divided these tumors into three types, a well-differentiated, an undifferentiated, and an intermediate or transitional group. Norris⁴ believed that it is impossible so to classify arrhenoblastomas because of the wide morphologic variations in individual specimens. Because of the widely variable histologic pattern of this tumor, it does not fit into any one of Meyer's groups.

There has been some discussion in the literature of the criteria for the diagnosis of arrhenoblastoma, and recent authors have been of the opinion that in the light of present knowledge both clinical and pathologic confirmation is required. The diagnosis in the case presented here is substantiated by the histologic examination of the tumor and by the clinical evidence of masculinization followed by resumption of feminine characteristics and regression of masculinization after excision of the tumor.

The sections stained with phenylhydrazine resulted in positive findings. This does not indicate the specific presence of corticosterones, but does suggest that in the tumor tissues are substances which are chemically consistent with the corticosterones or with similar substances which have been isolated from the adrenal glands but which have no cortical activity. Clinical laboratory methods for the determination of 17-ketosteroids in patients with arrhenoblastomas have yielded widely varying and inconclusive results. Several investigators, among them Frazer and Forbes,⁵ Talbot and Butler,⁶ and Mallory,⁷ report normal values. Recently Jones and Everett⁸ found increased values. It has been suggested by some authors that the virilizing factor in arrhenoblastoma is some steroid, not yet isolated, which is not a 17-ketosteroid. Kanter and Klowans⁹ found a markedly decreased blood and urinary sodium, which contrasts with the definite increase in blood sodium values reported by Cutler, Power, and Wilder¹⁰ in patients with the adrenogenital syndrome. Other laboratory procedures have proved to be of little value.

The multiplicity of tissue elements demonstrated in the histologic examination of this tumor suggest a possible teratomatous origin. Krock and Wolferman¹¹ in a review of seventy cases in the literature report that in twenty-four, or 34 per cent, tridermal tissue elements were found. When it is considered that the majority of arrhenoblastomas are large, and that most histologic studies are based on a very small portion of the tumor, the percentage of reports of teratomatous elements might be appreciably higher if the entire tumor were studied histologically. The work of many other authors, including Curtis,¹² Hartz,¹² and McLester,¹⁴ has supported the teratomatous theory.

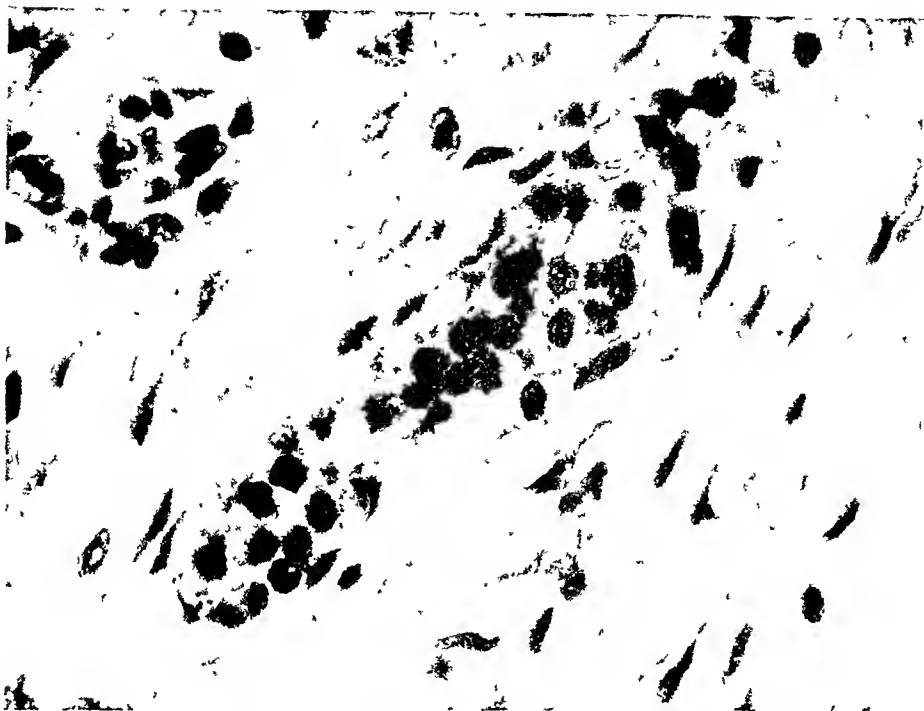


Fig. 3.—Interstitial cells, resembling the Leydig cells of the testes, are found throughout the tumor wherever there is loose connective tissue.



Fig. 4.—Gland structures lined by tall columnar epithelium and goblet cells (arrow) are seen in some regions. In the lumina of the glands is a mucoid substance.

The manner in which arrhenoblastoma and other hormone-producing ovarian tumors produce changes in the secondary sex characters of their hosts is not known. That the solution to this problem lies in endocrine interrelationships is emphasized by the experimental work on intersexuality done by Greene,¹⁵ Crew,¹⁶ and Lille.¹⁷ Other clinical and experimental reports indicate the involvement of the pituitary gland, although the significance of this fact is not clear. Huffman¹⁸ concluded that the androgenic effect of the male sex hormone given by injection produces changes in the female genitals which are secondary to pituitary changes, and that these effects last for only a short time after androgenic stimulation is discontinued. Huffman¹⁹ also substantiates the work of Hamilton and Wolfe²⁰ on basophilic changes in the pituitary gland after injections of testosterone propionate. There is also clinical evidence of pituitary involvement. Similar basophilic pituitary changes were found at autopsy in the case of arrhenoblastoma reported by Norris.⁴ Canelo and Lissner²¹ report a case of arrhenoblastoma which presented clinically many of the metabolic changes associated with Cushing's syndrome. These same metabolic changes, according to Kepler and his associates,²² are an integral part of the clinical picture of the masculinizing adrenal-like tumors of the ovary. Whether or not this close association of masculinizing ovarian tumors with the pituitary gland is significant, or whether it is merely incidental to the production of a virilizing hormone by the tumor, is not known.

Summary

1. A case of arrhenoblastoma of the ovary is presented with the diagnosis based on a combination of clinical and pathologic features.
2. The multiplicity of tissue elements found on histologic examination of the tumor suggest the possibility of a teratomatous origin.

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STERILIZATION FAILURE WITH EXTERNAL MIGRATION OF THE OVUM*

IRVING F. STEIN, M.D., MELVIN R. COHEN, M.D., AND RALPH ELSON, M.D.
CHICAGO, ILL.

(From the Michael Reese Hospital)

METHODS of tubal sterilization have varied widely from occlusion of the uterine ostium to various techniques of ligation (with and without crushing), tubal section, excision, and closure or burial of the fimbriated extremity. Few of them have stood the test of time without some failure. For a number of years we practiced the Walthard (Madlener) method until some failures were encountered. Then, after witnessing the technique used by Norman Miller of Ann Arbor, that of double tubal ligation of short loops without crushing, we tried that over a period of the past five years. We found the method entirely successful until we encountered this case which we suspected was a failure until proved otherwise at operation, as reported below. We have had, however, one other case of failure with this technique.

Polak reported a case of intrauterine pregnancy in 1910 which occurred after double salpingectomy. He took occasion to remark about "the vagaries of the fecundated ovum in selecting a location for its development, and the persistency and penetrability of the spermatozoon in its effort to reach the object of its search." Although not the first to be reported, his case serves to emphasize the fact that there have been pregnancies occurring after almost every type of tubal sterilization. Pregnancy has been reported even after supracervical hysterectomy.

The following case of sterilization failure is of interest because pregnancy occurred after double tubal ligation on the one side, eleven years after salpingo-oophorectomy had been performed on the other.

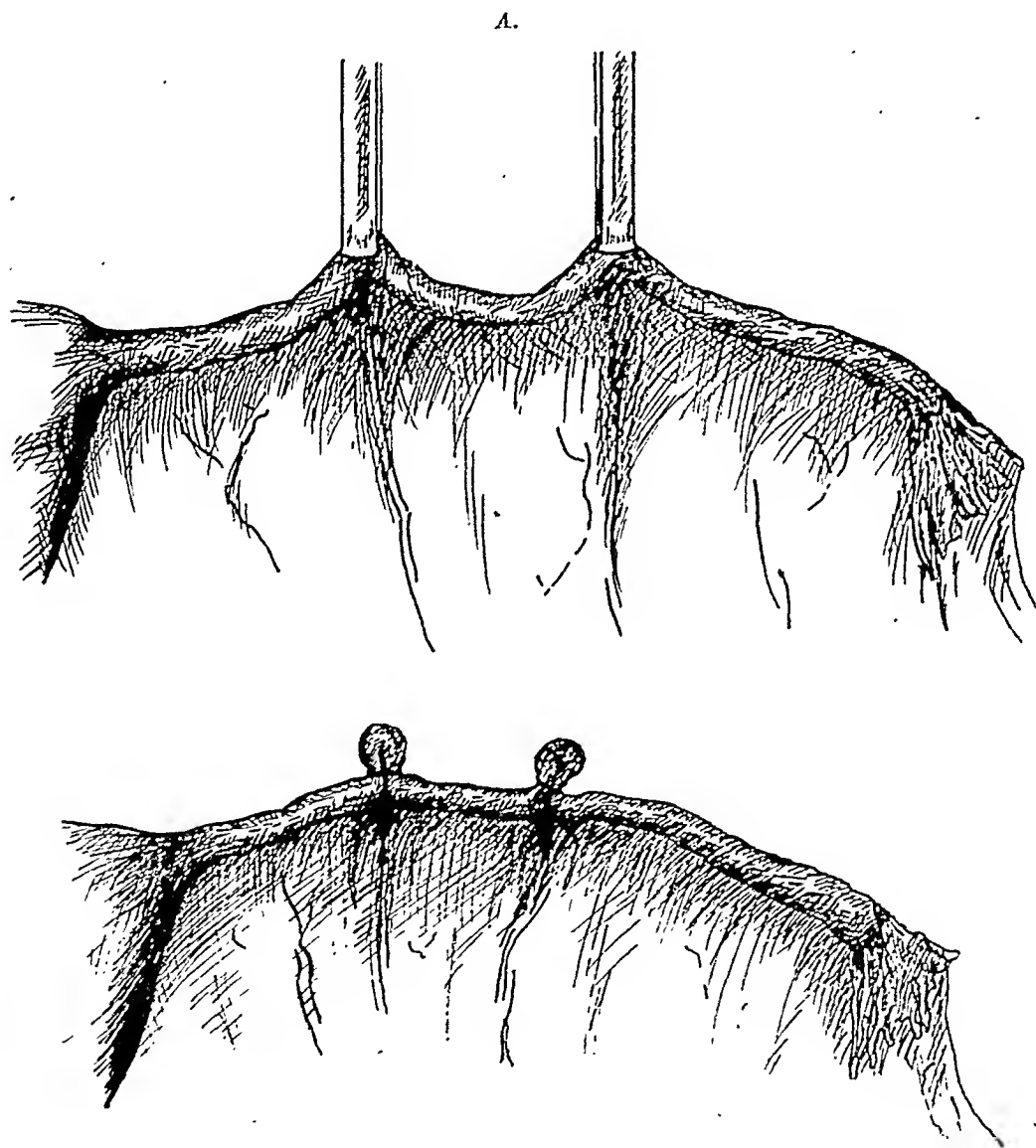
Case Report.

Mrs. A. N., aged 40, gravida iii, was first seen by us in 1938. Her menstrual history was normal, regular every 28 days, 2½ days' duration, scant in amount. Appendectomy and right salpingo-oophorectomy were performed in 1933. In 1936, she had delivered premature twins (seven months) which did not survive, and in 1937 a full-term stillborn breech. A third degree tear occurred during the extraction of the breech resulting in a rectovaginal fistula. Both of these confinements were cared for elsewhere, before we had been consulted. She first came under our care for her third pregnancy which was terminated on March 17, 1939, by elective low cervical cesarean. This was her first living child.

She again became pregnant in 1943 and a second elective low cervical cesarean was performed on May 17, 1944. At operation, the right uterine horn

*Presented before the Chicago Gynecological Society, March 21, 1947.

from which the adnexa had been removed in 1933, was covered with dense adhesions. A loop of the small intestine was found adherent, forming a sharp kink. The adhesions were freed and the bowel liberated. Sterilization was performed by catgut ligation of two small loops of the left tube, without crushing, according to the method described above. (Fig. 1.)



B.

Fig. 1.—Diagrammatic illustration of method of double tubal ligation for sterilization.

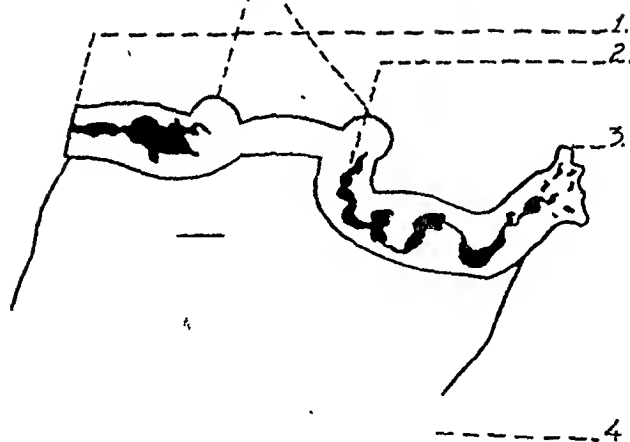
The patient was again seen on Jan. 15, 1945, complaining of amenorrhea, and she was found to be pregnant. The biological test was positive. Contrary to our advice, the patient obtained an induced abortion on Feb. 3, 1945. Subsequently, she returned to us for repair of the rectovaginal fistula, and requested that she be sterilized once more.

On May 18, 1945, she was operated on by one of us (I. F. S.) at Michael Reese Hospital. Because of the need for vaginal plastic repair and closure of the rectovaginal fistula, it was decided to approach the left tube through the

A.



Tubal Ligation

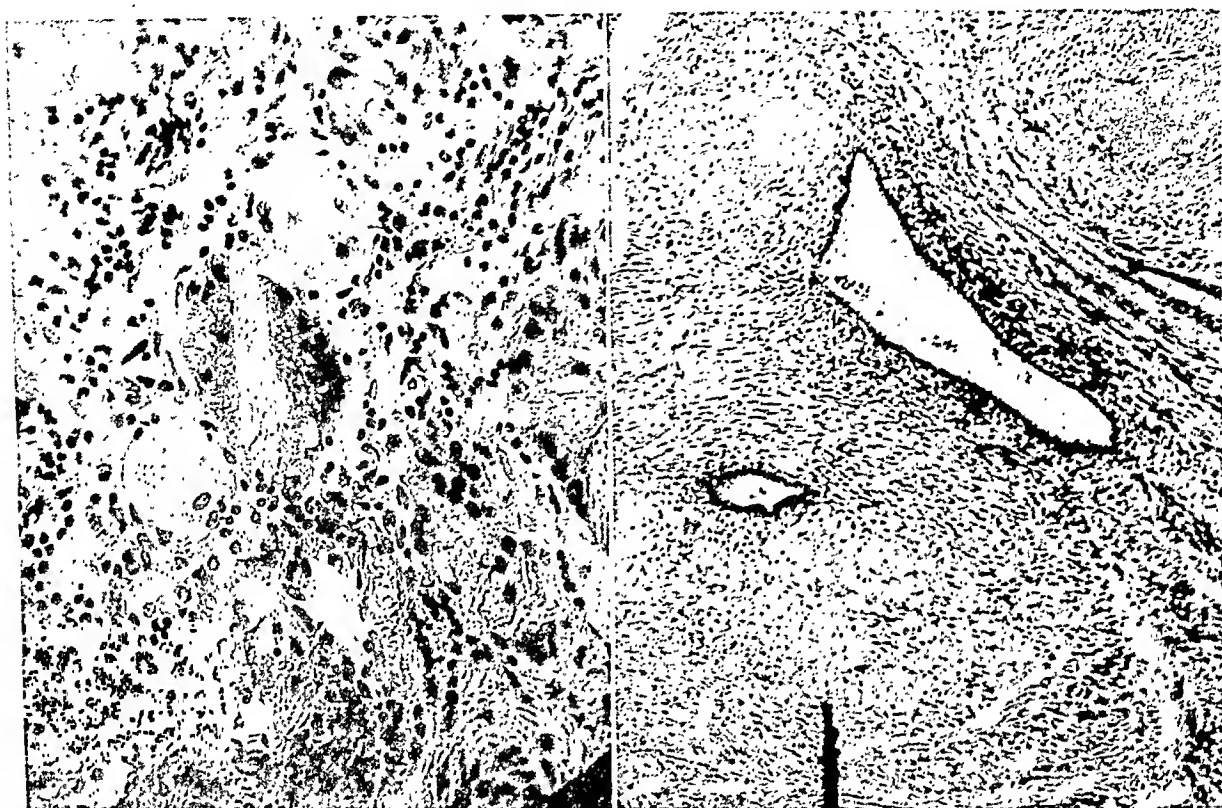


1. Cornual End of Tube
2. Opaque Medium
3. Fimbriated End of Tube
4. Ovarian Cyst

B.

Fig. 2, A. and B.—Opaque medium instilled into both ends of excised tube showing adequate sterilization by double ligation.

anterior cul-de-sac. Technical difficulties arose in attempting to reach the tube for sterilization and, therefore, vaginal hysterectomy and left salpingo-oophorectomy were performed. The following is a description of the operation:



A.

B.

Fig. 3.—Two cross sections of tubal lumen visualized. A. Complete obliteration by fibrosis after tubal ligation. B. Patent lumen in right uterine horn eleven years after salpingo-oophorectomy.

Under low spinal anesthesia (Pontocaine) the cervix was brought down and an attempt was made to separate the bladder from the uterus. In so doing, the bladder, which was extremely adherent (after two low cesarean operations) was inadvertently opened. The bladder was then completely mobilized from the uterus by scissors dissection and the laceration repaired with three rows of fine catgut. The anterior cul-de-sac was then opened and the uterus and left adnexa were extirpated. The entire left adnexa were removed because of an ovarian cyst measuring about 3 by 4 cm. with adhesions between the tube and ovary (the right adnexa had been removed eleven years previously). The vaginal vault was then suspended by corner stitches placed in the round and uterosacral ligaments. The peritoneum was closed with fine catgut and the vaginal vault closure completed with interrupted circle stitches of No. 1 catgut, leaving a small wick of sulfathiazole gauze draining the subvesical space. For repair of the rectovaginal fistula, a V-shaped flap was removed from the posterior vaginal wall, the region of the levator ani muscles exposed, and the repair carried out, bringing the small fistulous opening toward the perineum. The fistulous tract was excised and the tissue closed over it in layers. The perineal skin was approximated with interrupted plain catgut No. 0 stitches. A retention catheter was left in the bladder.

The patient made an uneventful recovery, completely relieved of both her old rectovaginal fistula, the recent (operative) vesicovaginal fistula, and she was finally adequately sterilized.

We had assumed that this was an instance of a failure of tubal ligation, the first we had encountered by the method of double ligation which we have described and illustrated. X-ray of the excised tube and pathologic examination of the removed organs revealed the following: the left tube when tested with opaque medium (lipiodol, Fig. 2) was found to be nonpatent. Upon injecting the uterine end of the excised tube with the opaque medium, it stopped at the first ligation. Injection into the fimbriated end was likewise found to be limited by the second ligated loop. Hence the tubal sterilization had been entirely successful. Furthermore, serial sections of the left tube confirmed the fact that continuity of the lumen was interrupted by the formation of fibrous tissue so that sterilization performed at the time of the second cesarean operation was competent. (Fig. 3A.)

With the double obstruction of the left tube clearly proved, the only possible way that an ovum could enter the uterus would be through the right cornu, the site of the previous right salpingo-oophorectomy. Therefore, serial sections were taken through the right cornu of the uterus. The interstitial portion of the right tube proved to be patulous. (Fig. 3B.)

The mechanism of conception in this case was obviously by means of external migration of the ovum. The right ovary and tube had been removed previously and the left tube had been successfully ligated. Therefore, the ovum, either before or after fertilization, entered the uterine cavity through the patent interstitial portion of the right tube.

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ENDOMETRIOSIS OF EPISIOTOMY SCAR*

HERBERT E. SCHMITZ, M.D., CHICAGO, ILL., AND PAUL GROSSBARD, M.D.,
PASSAIC, N. J.

(From the Department of Gynecology, Cook County Hospital)

ENDOMETRIOSIS is by no means a rare condition, and the sites in which endometrial tissue can implant itself are numerous: the ovaries, bowel, appendix, abdominal scars, etc. However, endometriosis in the perineum is extremely unusual. Schickel¹ in 1923, reported on the first case of perineal endometriosis. Neuwiller² in 1926 and Prager² in 1932 reported cases of perineal endometriosis following a perineal laceration resulting from a delivery. In 1933, Maliphant² reported a case following a colpoperineorrhaphy. Weiss and Synephia² in 1934 reported two additional cases of perineal endometrioma. In 1941, Jessing³ reported a case following a curettage and operation for prolapse. Micholitsch² reported a case of endometriosis in an episiotomy scar appearing several weeks following a forceps application.

The case to be presented we believe to be the first one reported following a normal spontaneous delivery.

Mrs. L. W., a 23-year-old Negro female, hospital number 45-36684, was admitted to the Cook County Hospital, Sept. 4, 1945. She was a para i, gravida ii. In 1940, the patient had a spontaneous abortion of a four and one-half-month fetus. In 1941 she had a normal spontaneous delivery of a full-term infant weighing 7 pounds 2 ounces, at which time a left mediolateral episiotomy was performed. It was repaired in layers using interrupted black silk sutures for the skin. Her postpartum course was uneventful and she was discharged on the tenth postpartum day in good condition.

On her present admission to the hospital she complained of marked pain and swelling in the region of her episiotomy scar. The pain and swelling recurred every month with the onset of her menstrual period, and would be relieved when the flow stopped. She had noticed this particularly in the last year but she had similar discomfort since about five to six months after her delivery.

On examination of the perineum there was evidence of a healed left mediolateral episiotomy scar. A hard mass was palpable the whole length of the scar. It measured 5 by 2 cm., was attached to the skin and underlying tissue. It was not particularly tender. A diagnosis of endometrioma was made.

On Sept. 11, 1945, the old scar and the mass were completely excised. The mass was found to extend down to the levator fascia.

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Fig. 1.—Section of the excised episiotomy scar.



Fig. 2.—Another section of the excised episiotomy scar.

Grossly, many blue pinpoint nodules were seen. Microscopic examination of this tissue showed endometrial glands and stroma. The diagnosis of endometriosis occurring in an episiotomy scar was confirmed.

Follow-up observation revealed the wound was well healed, and the patient had no further complaints of pain or swelling.

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PENTOTHAL SODIUM ANESTHESIA FOR CESAREAN SECTIONS

F. L. HERRICK, M.D., NEW HAVEN, CONN.

(From the Department of Anesthesia, Grace Unit, Grace-New Haven Community Hospital)

THERE are many articles in the literature relating to the use of Pentothal sodium in obstetrics, but few of them more than mention its use as the anesthetic for patients undergoing cesarean section.

Kassebohm and Schreiber¹ state that they have never been able to perform cesarean sections with either Pentothal or Evipal. Since publishing their paper in 1938, they have changed their views and find that they can use Pentothal if they have a competent, well-trained anesthetist to administer the anesthesia. Hellman, Shettles, Manahan, and Eastman² list its use in 114 cases and state, "It is quite adequate for cesarean sections."

At Grace Unit of Grace-New Haven Community Hospital, from 1942 to 1946, there were 492 cesarean sections performed using Pentothal as the sole anesthetic agent until after delivery. In practically all of these cases, it was the main anesthetic agent throughout the operation, supplemented with a mixture of equal quantities of oxygen and nitrous oxide after delivery of the child. The work is still going on, and it is hoped that a subsequent paper may include these later cases.

As was customary in 1942, this series was started using a 5 per cent solution of Pentothal, but in 1943 this was changed to a 2.5 per cent solution, and this is the concentration which has been used since. It is interesting to note that the total dosage of the 5 per cent solution in these early cases was much larger than is our present total dosage, sometimes as much as 2.5 Gm. being used. It was not supplemented, however, with oxygen and nitrous oxide. This serves as a good example, I believe, of the advantage of using some supplementary anesthetic to cut down the total dosage of Pentothal. No doubt some of the decrease is also due to an increased skill in administration which comes with experience in a large number of cases.

It seems to me that, from the viewpoint of the mother, there is a definite advantage in this form of anesthesia. Since she is asleep, she is spared the apprehension which would be experienced if, for any reason, the baby should not cry promptly. Induction is very quick, quiet, and pleasant. Unconsciousness is attained within twenty to thirty seconds, and, in most patients, if the surgeon is not too timid about making the skin incision even though there is some pain reaction, the operation may proceed within one to one and one-half minutes after the anesthesia started. Incidentally, I have never had a patient who has remembered any pain of incision even though many of them react when the skin incision is made.

The anesthesia is so pleasant for the patient that most of them ask for it now when seen by the anesthetist before operation. In fact, if the patient has to have a subsequent operation for some other condition for which it is felt that Pentothal is not the anesthetic of choice, it is very difficult to convince her of this. This may be regarded as a disadvantage in some patients.

As pointed out by Hellman,² Pentothal passes through the placenta, reaching equal concentration in fetal and maternal blood within ten to twelve minutes. There is apparently a period of five to eight minutes, however, after starting the anesthesia, during which the amount of the drug reaching the fetus is very small. This point should be borne in mind by the operator doing an occasional cesarean, I believe, since the margin of safety for the fetus may be too narrow in his hands.

Since the average time from the start of anesthesia to the delivery of the baby was 8.83 minutes, we were well within the safety period. This includes the patients operated upon by the resident staff and the occasional one by the general surgeon, which brings the average time up considerably. Another factor which raises it, is the inclusion in this series of a fair number of Waters' sections, although most of the operations were of the low-flap type. In most cases done by the attendings on the obstetric service, the fetus is delivered in between four and six minutes after the start of anesthesia.

In this series, there were 48 mothers, or 10 per cent, who had either nausea or nausea and vomiting postoperatively. Practically all of these had only nausea, and the occasional ones who did vomit usually did so only once or twice. The average time for the mother to react from the anesthetic was figured as 28.7 minutes. Actually this is too high, however, since the time was figured from the time that the operation was finished to the time the patient first required something for the relief of postoperative pain, except for those who were reacting when they left the operating room. There were 106 of these, which is 21.5 per cent.

There were no maternal deaths. Thirteen, or 2.7 per cent, of them had atelectasis, which, in every case but one, was mild. Since many of these patients who were operated upon as emergencies had some respiratory infections, and others had had a recent meal, it is surprising to see that this figure is not higher. It is not our practice to operate upon patients who have an upper respiratory infection, but when a patient requiring a cesarean section goes into labor, we have no choice.

There were 15 fetal deaths or 3 per cent. These were patients in whom the fetal heart was heard prior to induction of anesthesia. The causes of death in these 15 infants are listed in Table I.

TABLE I. FETAL DEATHS—FETAL HEART HEARD PRIOR TO THE INDUCTION OF ANESTHESIA

Prematurity	7
Erythroblastosis	1
Atelectasis	5
Congenital heart disease plus atelectasis	1
Cerebral anoxemia	1

There were only five of these deaths in which it is felt that the anesthetic may have had an adverse effect on the fetus. All of these were cases in which, due to a prolonged induction time or too slow delivery of the baby or both, we

went over the safe period. No doubt the Pentothal was of about equal concentration in both maternal and fetal blood.

It is felt that some of these infants might have been revived had more expert resuscitation been available. Too often this art is left to the family physician or an inexperienced intern. This was especially true during the war years, which is the period covered in this report. Adequate, well-trained help was scarce during that period. Those to whom this important task was assigned did their best, but, unfortunately, they had not had sufficient experience in the use of the resuscitator.

There is also more to the proper sucking-out of the pharynx in a newborn infant than in an adult. Too often some well-meaning person, in attempting this procedure, will put a large finger down the infant's throat in an attempt to get the suction tip in close proximity to the larynx. Suction is doubtless fairly efficient, but the finger is filling the entire pharynx and thus obstructing the first feeble attempts of the infant to inhale. My opinion is that this important procedure should be intrusted to that person who is best trained in its use.

There were 331 or 70 per cent of the infants who cried spontaneously. The remaining 139 or 30 per cent were resuscitated by means of suction plus oxygen under slight pressure. There were 27, or 5.7 per cent, who required oxygen after admission to the nursery. All of these were premature with the exception of those who had some congenital anomaly such as those listed in Table I.

Technique

The night before operation on an elective-cesarean patient, she is examined by the medical anesthetist, and Nembutal—grains $1\frac{1}{2}$, is given. One hour before operation, she is given atropine, grain $1/150$ by hypodermic.

Upon arrival in the operating room, the patient is catheterized and placed in position on the operating table. Her pulse, blood pressure, and respirations are checked by the anesthetist. The abdomen is painted and draped.

As the last drapes are being put on, the Pentothal is started, 2 to 3 c.c., followed by about a thirty-second wait to watch the effect. The Pentothal injection is then continued slowly but steadily while the depth of the respirations, the lid reflex, and movement of the eyeballs are carefully watched. As the anesthesia approaches the third plane, the surgeon tests the reaction of the patient to pain by pinching the skin with an Allis clamp. If there is only slight reaction, the incision is made. Oxygen by mask connected to the anesthesia machine is started at the same time as the operation, or before, if there is a lag in reaching the desired depth of anesthesia. Usually it requires between 400 and 500 mg. of 2.5 per cent Pentothal before the operation can be started. Occasionally, a patient may require between 500 mg. and 1 Gm. As soon as the infant is delivered, 1 c.c. of Ergotrate is given intravenously to the mother and either nitrous oxide is added to the oxygen in an equal quantity, or, if it seems more desirable, the Pentothal may be discontinued and the operation finished with cyclopropane and oxygen. We are rather more likely to do the latter if the patient has required over 500 mg. of Pentothal for delivery of the baby.

Conclusions

It is not claimed that this is the only safe anesthetic or even the safest anesthetic for this operation. In our hands, however, we feel that it has definite advantages in most patients.

1. I still maintain, however, that the choice of anesthetic for such cases should be based on the following facts:

1. Condition of the patient.

2. Skill and training of the anesthetist.
3. Operative skill and experience of the surgeon.

We must never forget, in cesarean sections, that we have two or more lives to consider, instead of the one involved in other surgical operations.

Summary

The use of Pentothal sodium as the anesthetic in a consecutive series of 492 cesarean sections is reported. There were no maternal deaths. The incidence of nausea and vomiting was small. The 2.7 per cent atelectasis may at first thought seem high, but when it is considered that many of these operations were done as emergencies, it takes on a much less serious aspect.

There were 15 fetal deaths, only 5 of which may have been due in any respect to the anesthesia.

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COMBINED LOCAL INFILTRATION ANESTHESIA AND PENTOTHAL SODIUM ANESTHESIA IN CESAREAN SECTIONS

A Preliminary Report

JULIUS A. FINO, M.D., AND JOSIAH R. EISAMAN, M.D., PITTSBURGH, PA.

(From the Department of Obstetrics, University of Pittsburgh School of Medicine and the Elizabeth Steel Magee Hospital)

THE use of local infiltration anesthesia in any surgical procedure has decreased the dangers associated with a general anesthetic by decreasing the effects of anesthetic agents on the vital nerve centers. In abdominal surgery, local infiltration anesthesia in conjunction with general anesthesia has been useful in assuring good muscular relaxation. General anesthesia in cesarean sections has long been a disputed question because of fetal narcosis.

There is a certain amount of apprehension caused in the patient when local infiltration anesthesia is used alone in abdominal surgery or in cesarean sections. This has been minimized in many instances by combining local anesthesia with analgesia such as nitrous oxide and oxygen or by using morphine sulfate and scopolamine hydrobromide but, again, in cesarean sections fetal narcosis may be produced. If the operative procedure should take longer than contemplated, apprehension again appears, accompanied with some discomfort to the patient.

Pentothal has become a favorite anesthetic in general surgery but in cesarean sections its disadvantages are evident because of the narcotic effect on the infant, necessity for rapid delivery, and its limitations to the elective type of cesarean section only.

We have combined local anesthesia and nitrous oxide analgesia with intravenous Pentothal sodium. Pentothal sodium was chosen because of its rapid and smooth induction and its relative safety as an anesthetic agent when used properly.

In obstetrics there are such complications as placenta previa, the toxemias, fetal distress, or cephalopelvic disproportion, in the presence of an upper respiratory infection in which a general anesthetic may be harmful to both the mother and the infant. With these complications and the relative safety of both the mother and the infant in mind, we have used a simplified technique of local infiltration anesthesia associated with intravenous Pentothal sodium.

Technique

Tissue trauma and haste must be avoided for a successful result.

A 1 per cent solution of Novocaine, without Adrenalin hydrochloride, is used throughout the procedure. It may be necessary to use nitrous oxide

analgesia while carrying out the technique to allay the apprehension which may occur in the patient. The use of 50 to 100 mg. of Demerol preoperatively has been very helpful and also less depressing to the infant.

1. The operative site is directly infiltrated with Novocaine; this includes infiltration of the dermis. An initial wheal is made using a 26 gauge needle. This is preferably made at a point midway in the contemplated length of the incision. The entire infiltration may be successfully made through this point by using a 4 inch, 20 gauge needle and constantly moving the needle while infiltrating the dermis.

2. The subcutaneous tissues are then infiltrated down to the fascia.

3. Perpendicular punctures of the abdomen are then made penetrating the fascia. These punctures are approximately 1 inch to 1½ inches apart and the fascia and underlying musculature are infiltrated with Novocaine.

4. After a few minutes' wait, the skin is incised down to the fascia. Hemostasis is assured and all bleeding points are ligated. During this delay the fascia and the muscular tissue directly beneath the fascia become anesthetized.

5. The fascia is then incised. This is best carried out by using the scalpel. This prevents the pressure and tearing effect caused by using scissors.

6. The recti muscles are infiltrated laterally to the outer borders of their respective sheaths. A 4 inch, 20 gauge needle is used; infiltration points are approximately ¾ inch apart and the needle is moved constantly during the infiltration. By following this procedure, both the anterior and posterior branches of the thoracic nerves which supply the anterior abdominal wall are anesthetized. The underlying preperitoneal tissues are also anesthetized.

7. The edges of the abdominal incision are draped with sterile towels and the peritoneum is directly infiltrated with Novocaine. This is incised and the preperitoneal tissues laterally, including the posterior portion of the rectus sheath, are again infiltrated using the technique as described above. Relaxation is assured and the uterine wall is exposed. No packs are inserted into the abdominal cavity to wall off the uterine incision. Retractors may be used if found necessary.

8. The uterus is centered or adequately exposed, Pentothal anesthesia is started, and the uterus is then opened. In low cervical cesarean sections the Pentothal anesthesia is started following infiltration and dissection of the vesical fold.

Local infiltration of Novocaine and intravenous Pentothal sodium anesthesia were used in a group of 40 patients. There were 16 primiparas and 24 multiparas.

The indications for cesarean section were as follows:

Bicornate uterus, elderly primipara	1
Cephalopelvic disproportion	16
Diabetes mellitus	2
Pulmonary tuberculosis	1
Toxemia of pregnancy	2
Fetal distress	2
Previous cesarean section	7
Previous myomectomy, no viable infants	1
Placenta previa	1
Placenta previa, multiple pregnancy	1
Surface carcinoma of cervix	1
Inertial labor	2
Previous extensive vaginal repair	2
Rheumatic heart disease	1

There were twenty-seven classical cesarean sections; this included four cesareans with a high uterine incision. There were thirteen low cervical cesarean sections. An incisional hernia was repaired in one case. In five cesareans, lysis of adhesions and appendectomies were performed. An ovarian cyst was removed during one laparotomy.

The length of time from the beginning of the infiltration of the Novocaine and the extraction of the child varied from nine to thirty minutes; the majority of the infants were delivered within fifteen minutes. This variation in time was due to the degree of sensitivity to pain found in some of the patients.

The average amount of Pentothal used was 12.4 grains; 5 grains were used in one case and the maximum was 30 grains. The majority of the patients required only 11 grains of Pentothal sodium. Intravenous Pentothal sodium was given after completion of a classical uterine incision in 6 patients. In 9 patients the time interval was one minute before the birth of the child. Intravenous Pentothal was given two minutes before the birth of the infant in 12 patients. In 7 patients the time interval varied from three to six minutes. In 2 patients the time interval was seven minutes from the time the Pentothal was given to the birth of the infant.

Atropine sulfate, gr. $\frac{1}{150}$ (0.4 mg.), was the only premedication in 17 patients. Demerol with atropine sulfate was given preoperatively in 22 patients; 2 patients received 50 mg. of Demerol; 4 patients received 75 mg. of Demerol and the remaining 15 patients received 100 mg. of Demerol. One patient received morphine sulfate, gr. $\frac{1}{6}$ (11 mg.), and atropine sulfate preoperatively. Nitrous oxide analgesia in small amounts with continuous oxygen was used during the operation with all the patients.

The length of time from the first infiltration of the operative site to the completion of the operation varied from thirty to seventy-four minutes. The average time was forty-seven minutes.

Complications

A mild laryngospasm occurred in one patient. This patient was a gravida iii, para ii. Her first pregnancy terminated spontaneously. The second pregnancy was terminated by a cesarean section because of a severe pre-eclampsia. Her third pregnancy was terminated by a classical cesarean section and the fallopian tubes were ligated by the Madlener technique. The patient was administered 100 mg. of Demerol and $\frac{1}{150}$ grain (0.4 mg.) atropine sulfate preoperatively. The length of time between infiltration of the abdominal wall and the birth of a viable infant was seventeen minutes. The infant was delivered two minutes after the injection of Pentothal sodium. Three minutes later a mild laryngospasm occurred followed by an excessive amount of vomiting. A total of 25 grains of Pentothal sodium was used during the operation. The post-operative course was uneventful.

Results

1. There was no fetal or maternal mortality in this series of patients.
2. There was delayed fetal respiration in two cases. In these cases, seven minutes elapsed from the beginning of the Pentothal anesthesia to completion of the delivery of the infant. All of the remaining infants breathed spontaneously. Thirty per cent of the babies began crying as soon as the head was delivered through the opening in the uterus.

3. As far as it is possible to determine with this small series, Demerol preoperatively had no effect on the infant. Its analgesic action to the patient was gratifying.

4. Pentothal sodium given immediately before the incision in the uterus allows for unobstructed and rapid delivery of the infant with no effect to the infant and no discomfort to the patient.

5. The immediate postoperative condition of the patients was satisfactory. There was no abnormal nausea or vomiting. Actually, the postoperative reaction of the patient seemed to be superior to that with other forms of inhalation anesthesia. This was augmented by giving the patients 100 mg. of Demerol immediately upon showing signs of reacting from the anesthetic.

Summary

Carefully combined local infiltration anesthesia and Pentothal anesthesia give excellent results in cesarean section (both mother and infant) providing undue haste and tissue trauma are eliminated.

RECTAL HEMORRHAGE FOLLOWING IRRADIATION FOR CARCINOMA OF CERVIX

JAMES R. JOHNSTON, M.D., F.A.C.S., PITTSBURGH, PA., AND
HAROLD W. JACOX, M.D., NEW YORK, N. Y.

(From the Tumor Clinic of The Western Pennsylvania Hospital)

LATE intestinal complications following irradiation for pelvic malignancy are recognized and frequently anticipated. There are degrees of damage to the distal colon, varying from the mildest type causing a simple proctitis, through stages of destruction terminating in atrophy, stenosis, or perforation. These changes often are on the basis of obliterative endarteritis or telangiectasia. Rectal hemorrhage frequently responds to medical treatment or to colostomy. Relatively few cases require colostomy, but when necessary, it is usually entirely effective in relieving the condition.¹ We report a case of severe, intractable rectal hemorrhage following radiation therapy for recurrent carcinoma of the uterine cervix which necessitated not only colostomy, but even excision of the distal sigmoid and rectum to stop the hemorrhage. We have not found a similar case reported.

In addition, thirteen months later, this patient developed a primary carcinoma of the ascending colon which was resected, and the patient remains in normal health seven years later, without evidence of recurrence of either neoplasm.

Mrs. I. H., aged 47 years, weight 132 pounds, and the mother of one child, gave a history of having "a growth removed from the uterus" in April, 1935. In April, 1936, she had a uterine hemorrhage. Her physician stated the pathology report showed no carcinoma, but she received a small exposure (amount not given) of radium in the cervix and fundus. In March, 1937, she had recurrence of vaginal bleeding and a biopsy showed carcinoma of the cervix. She had more radium, reported to be a 50 mg. focus for forty-eight hours, or 2,400 mg. hr. She was then referred to our clinic for x-ray treatment. She received a series of high voltage (200 kv. 0.5 mm. Cu) x-ray treatments to a total of 1,600 r. (measured in air) to each of four pelvic portals 12 by 17 cm. in size, over a period of sixteen days. This was given at the daily rate of 200 r. to each of two portals, alternating front and back. Biopsy after the x-ray series showed no neoplastic cells present.

In September, 1937, she complained of a yellowish vaginal discharge. A biopsy of the cervix showed papillary adenocarcinoma. She was treated with radium consisting of two 40 mg. capsules (with 1 mm. platinum filtration) tandem in cervix and fundus and four 10 mg. needles (0.5 mm. platinum) in the parametria for thirty hours, giving a total of 3,600 mg. hr. This was followed in ten days by x-ray treatment with the same technique as before, totalling 1,400 r. to each of four portals over a period of fourteen days.

In April, 1938, there was moderate bleeding from the rectum. In September, this bleeding was more profuse and she was admitted to the hospital Oct. 4, 1938. The red blood cell count dropped steadily from 3,020,000 to 2,450,000 even though she had two transfusions. A colostomy was performed on Nov. 4, 1938. Following this the bleeding continued and the red blood cell count fell to 1,450,000. Since conservative treatment failed, it was then deemed advisable to do a resection of the sigmoid and rectum. After several transfusions, this was

done on Jan. 4, 1939. The pathology report of excised bowel was as follows: "A section of sigmoid and adjacent descending colon was received. The entire specimen measures 23 cm. in length and has an average circumference of 4 to 4½ cm. The distal 6 cm. of the bowel is indurated. This induration involves not only the mucosa and submucosa but also the appendices epiploicae. The mucosa in this segment presents a fiery red, finely granular appearance and is definitely depressed from the remaining smooth, velvety, pink mucosa. The remainder is normal in consistency. The wall in the indurated area is rather thicker than average and the mucosa here has lost its normal haustrations. On careful examination of the mucosa, a number of small diverticula can be demonstrated in its proximal one-third. The lower one-third possesses a smooth mucosa that shows a great number of minute, distended blood vessels.

"*Microscopic:* Section through the granular portion of mucosa of the distal segment exhibits a fibrous type of granulation tissue in which a small number of isolated, large cells are found. These cells vary in size and shape, possess gigantic, almost black-staining nuclei and occasionally an acidophilic nucleolus about 7 microns in diameter. The mucosa here is completely absent. The granulation tissue is heavily infiltrated by inflammatory cells of all types. The muscularis is essentially normal. The serosa, in this as well as sections remade from this area, show fibrosis, foci of monocytic infiltration and foreign-body, giant-cell reaction. The mucosa elsewhere shows no striking change.

"*Diagnosis:* Metastatic carcinoma, undifferentiated in submucosa of colon. Extensive chronic ulceration of colon with cicatrization of submucosa."—*Dr. Paul Gross.*

The postoperative course was complicated by wound infection and thrombophlebitis of the left leg. She was discharged from the hospital Feb. 25, 1939, with a red blood cell count of 3,200,000 and a weight of 100 pounds.

She gained steadily throughout that year, but in January, 1940, a mass appeared in the region of the right colon which produced no symptoms. X-ray examination of the colon showed a constriction in the ascending portion suggestive of a new growth. Operation Jan. 30, 1940, consisted of resection of the ascending colon and hepatic flexure with lateral anastomosis of the cecum to the transverse colon. Histologic examination showed "undifferentiated carcinoma involving large bowel." She had an uneventful convalescence and gained steadily in weight. One year later, in January, 1941, her weight was 144 pounds. Her only complaint was frequent urination, due to a bladder capacity of 7 ounces. This condition persists to the present time.

The years 1942 and 1943 were uneventful.

In July, 1944, the patient had an attack starting with chills followed by high fever, and accompanied by an erysipelas-like eruption of the skin of the vulva, mons, and upper thigh. To date, April, 1947, she has had ten or twelve of these attacks. Sulfonamides brought the temperature to normal in two or three days, but in the past two attacks recovery was much quicker when 300,000 units of penicillin in oil and wax were given at the onset. Despite this complication the patient considers herself in excellent health.

Comment

This patient made remarkable recoveries from three potentially fatal conditions, namely, recurrent carcinoma of the uterine cervix, severe, intractable rectal hemorrhage due to irradiation and metastatic carcinoma, and a second primary carcinoma of the ascending colon.

The rectum was damaged from the large amount of irradiation required to control the cervical lesion. This type of rectal inflammation resulted in bleeding so prolonged and profuse, despite every known means of treatment, that life was endangered. The bleeding was from a smooth, granular surface without slough or erosion of sizeable vessels. The pathologic findings were those

of fibrosis with the presence of neoplastic cells. This may have produced hemorrhage by preventing the arterioles from contracting and was corrected only by resection of the bowel, thus permitting the long survival.

Incidentally, it is not often that microscopic changes of the entire bowel wall can be studied as in this case, because ordinarily only small pieces are obtained as biopsy specimens.

The lesion of the ascending colon probably was not a neoplastic extension or metastasis, because an x-ray examination fifteen months before showed that portion of the bowel to be normal. Even though a total of approximately 50 per cent of the colon was resected, the colostomy functions well and requires little attention.

The intermittent attacks of erysipeloid eruption of the pubic and perineal regions are probably related to partial lymphatic blockage which favors a low-grade, chronic inflammation. This is similar to the phenomenon in an edematous upper extremity following radical mastectomy. The etiology is unknown but the response to sulfonamides or penicillin is prompt.

The small capacity of the urinary bladder, in the absence of cystoscopic evidence of interstitial cystitis, is probably due to the fibrosis and contraction as a result of the extensive irradiation and surgery.

Summary

A 47-year-old woman who was treated twice with radium, followed by two pelvic x-ray series, for carcinoma of the uterine cervix, one year later developed severe rectal bleeding which required resection of the terminal large bowel. About a year after that, she developed a clinically silent primary carcinoma of the ascending colon which was treated surgically. Ten years after the cervical carcinoma and seven years after the cancer of the colon, she continues in excellent health without recurrence of either neoplasm.

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CERVICAL CANCER WITH METASTASIS TO BREAST

HAROLD SPEERT, M.D., AND ARTHUR V. GREELEY, M.D., NEW YORK, N. Y.

(From the Gynecological Service of the Roosevelt Hospital)

MAMMARY metastasis from carcinoma of the uterine cervix is either exceedingly rare or it has been overlooked. The literature contains several reports of cases in which malignant tumors appeared independently in the breast and cervix of the same patient (Smith and Bartlett, 1929; Cordua, 1929, 1936; Taylor, 1931; Schreiner and Wehr, 1934; Hellendall, 1935; Fernandez-Colmeiro, 1946; Taylor and Guyer, 1946). A case has also been recorded in which a probable metastasis to the cervix occurred in a woman with a primary mammary lesion (Eseh, 1929). We have been able to find references to only four cases, however, of primary cervical cancer associated with metastatic tumor in the breast. Three of these were mentioned briefly by C. Schroeder (1887) in a review of the previously published papers of six other authors. The fourth appeared in a summary of the material in the Pathological Institute at Kiel between 1914 and 1918 (Petzold, 1922). In none was the case described nor were photographs shown.

More recent studies of the sites of metastases from cervical carcinoma fail to list the breast among the organs affected. Among these studies are Meigs' report (1934) of 396 cervical cancers, and Griecouroff's analysis (1942) of 2,076 cases in the Curie Radium Institute. The following case is reported because it represents the first proved instance of metastasis to the breast from one of the commonest of all human tumors.

Mrs. A. L. was a 49-year-old white nulliparous divorcee. Her past history included a spontaneous abortion in 1915, appendectomy in 1928, tuberculosis with eight months' hospitalization in a sanitarium in 1930, and a membership in Alcoholics Anonymous. She complained of intermenstrual spotting in September, 1945, at which time biopsy of the cervix revealed epidermoid carcinoma (Fig. 1). A course of sixteen deep x-ray treatments was given between Oct. 1 and Nov. 5, 1945, the patient receiving 1,500 roentgen units to each of four pelvic portals. On Nov. 4, 1945, 140 mg. of radium was applied in and against the cervix for a total dose of 3,000 mg. hours. The patient was hospitalized again from March 5 to 15, 1946, because of pelvic pain and dysuria. Roentgenogram of the chest and intravenous pyelogram were negative. A mild cystitis responded to treatment with sulfadiazine and penicillin. She was readmitted on May 13, 1946, because of a sudden profuse vaginal hemorrhage, for which she was treated with vaginal packing and blood transfusion. Her final admission to Roosevelt Hospital was Nov. 15, to Dec. 14, 1946, when she complained of severe low back pain. The patient had lost much weight and appeared chronically ill. General physical examination was essentially negative, save for enlarged left supraclavicular lymph nodes and a small firm nodule, about 1 cm. in diameter, in the upper outer quadrant of the left breast. The tumor was superficial, but not attached to the skin. Pelvic examination revealed no evidence of the previously existent cervical tumor. Roentgenograms of the skull showed two areas of decreased density which were interpreted as metastases.



Fig. 1.—Cervical carcinoma.

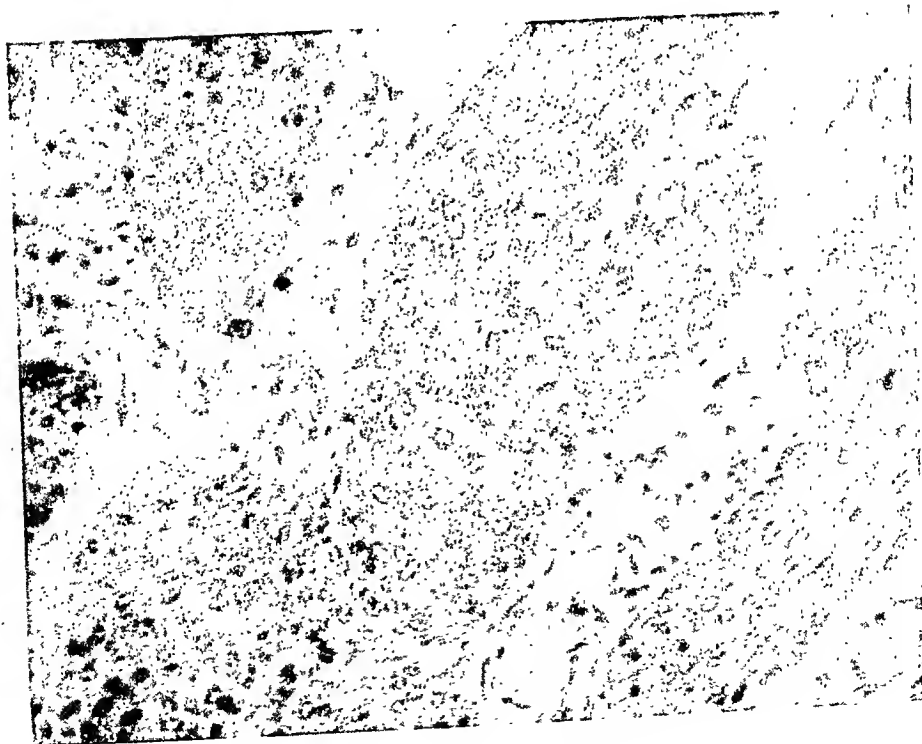


Fig. 2.—Metastasis in left breast.

Biopsy of the nodule in the left breast was performed on Dec. 6, 1946. Pathologic report was "metastatic epidermoid carcinoma in the breast" (Fig. 2). The histologic appearance of this tumor was identical to that of the original cervical biopsy. Unsuccessful efforts were made to control the patient's back pain with large doses of testosterone propionate (50 mg. daily) and with eobra venom. Requiring constant narcosis, she was transferred to a home for terminal care, where she died about Feb. 1, 1947.

Metastatic tumors of the breast are rare. Dawson was able to collect only ten cases from the literature in 1936 and added one of her own, a gastric carcinoma. This, then, represents the twelfth reported case of metastatic carcinoma in the breast. The infrequency of carcinomatous metastasis to this organ was responsible in part for Virchow's generalization (1863), long since disproved, that most organs which show a strong disposition to the development of primary malignant tumors are seldom the site of a secondary tumor.

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Note.—A recent tabulation of the sites of metastases in a series of patients who died with cervical carcinoma included another instance of metastasis of the breast. (De Alvarez, R. R.: *AM. J. OBST. & GYNEC.* 54: 91, 1947.)

33 EAST 68TH STREET

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

Dr. Trussell presents in this report, *Trichomonas Vaginalis* and *Trichomoniasis*,¹ the present status of our knowledge of trichomonas vaginalis. A tremendous amount of literature has been developed since this organism was first suggested as an etiologic factor in vaginitis by Hoehne in 1916, and Dr. Trussell has rendered a fine service in evaluating this material. More particularly, he has interested himself in the life history of the parasite, its growth requirements in attempting to produce a pure culture, its biochemical activities, and the effect of various physical and chemical agents on its viability and pathogenicity. He discusses not only the *T. vaginalis* but also the other parasites of a somewhat similar nature.

The second part of the book is an extended discussion of the infections caused by the parasite as to the location, source, recognition, prognosis, and clinical findings. Dr. Trussell does not feel from his own investigations that women harboring *T. vaginalis* have an increased tendency to a morbid puerperium.

Treatment, the author states, since 1916, has been a series of "trial and error" experiments. Much of the treatment, he says, has been based on a combined effort to eliminate not only the *T. vaginalis*, but also the associated abnormal microflora. Dr. Trussell feels that the two most effective methods of vaginal medication are powder insufflation and jellies, the latter adjusted to an acidity favoring normal vaginal biology. He states that as yet no specific therapeutic agent has been discovered and the various drugs and chemicals used in recent years are listed in some 59 pages. This multiplicity reflects the general lack of success obtained.

The book closes with a discussion of the taxonomic relationship of trichomonas to other protozoa, a parasite-host list of trichomonads, as well as a bibliography.

Studies of this type on the biology, growth requirements, and various relationships of the parasite should, one feels, soon lead to the discovery of a specific agent for the eradication of such infection which, while not as severe as similar infections in animals, still has a high nuisance value to both the patient and the clinician.

PHILIP F. WILLIAMS.

Dr. McCormick's fine monograph on *Pathology of Labor, the Puerperium, and the Newborn*² appears in its second edition with an increase of one hundred pages to include the advances and new techniques, while almost the same number of new illustrations have been added to correlate the added material. Among the major revisions is a discussion of the Caldwell-Moley classifications of the female pelvis. While acknowledging the tremen-

¹*Trichomonas Vaginalis and Trichomoniasis*. By Ray E. Trussell, M.D., Associate in Hygiene and Preventive Medicine, Former Research Assistant in Obstetrics and Gynecology, State University of Iowa, with an Introduction by E. D. Plass, M.D., Professor of Obstetrics and Gynecology, State University of Iowa, Charles C Thomas, Springfield, Ill., 1947

²*A Textbook Pathology of Labor, the Puerperium and the Newborn*. By Charles O. McCormick, A.B., M.D., F.A.C.S., Clinical Professor of Obstetrics, Indiana University School of Medicine, Consulting Obstetrician to William H. Coleman Hospital for Women, Indianapolis City Hospital, and Sunnyside Sanitarium, Second Edition, 492 pages, with 272 illustrations, including 24 in color, The C. V. Mosby Company, St. Louis, 1947.

dous help of pelvioradiography, Dr. McCormick feels that such studies must always remain secondary to clinical examination and judgment. The Burns maneuver for the delivery of the aftercoming head, which does not employ shoulder traction, and which avoids jaw flexion, is described and illustrated. It has been successful in the hands of the author.

Dr. McCormick, who is a firm believer in prophylactic external version in breech presentations, has rewritten this section, particularly with regard to technique. For impaction of the shoulder he describes a technique which has been found eminently successful in his clinic in recent years. This corkscrew maneuver undoubtedly would be useful in the occasional emergency of this nature. There is an excellent review, with concise directions as to treatment, of the anticoagulants in the prevention and treatment of deep thrombophlebitis.

The conflicting opinions as to the handling of the diabetic in labor are discussed in an expanded section on this topic. McCormick prefers vaginal delivery when possible. He stresses the availability for prompt treatment of shock and other situations which bring about sudden death during labor. In the excellent section of the book devoted to pathology of the newborn, the text regarding the Rh factor and hemolytic disease in its various manifestations is augmented. The author has pointedly advised checking the Rh situation in all obstetric transfusions.

An appendix carries a very thorough discussion of different types of pain relief in labor. The author concludes with the statement that analgesia and anesthesia must remain secondary to maternal and fetal welfare. The appendix also describes a series of puerperal exercises. In regard to the early ambulation of puerperal patients the author anticipates an increased amount of retroversion and prolapse of the uterus, and associated disturbances from this practice. From a psychological aspect he feels that a puerperal patient is not only entitled to, but profits by, extra days of hospital rest. The obstetric aspects of the Canon laws of the Roman Church are well included. Once again the reviewer is favorably impressed with the complete coverage of the three subjects in the title and the clarity and conciseness with which they are set forth.

PHILIP F. WILLIAMS.

In this excellent *Synopsis of Obstetrics*,³ now in its third edition, the author has added advances and rewritten five different subjects, yet by adhering to the original idea of a brief although adequate discussion, the book gained only twenty pages over the first edition. There is new material on the biologic hormone tests of pregnancy. An excellent review discusses the presently suggested methods of relieving pain in labor, and it is well that space has been given to the dangers, difficulties, and contraindications of the methods mentioned. Litzenberg has stressed the difficulties encountered with every type of pain control, in order that caution instead of enthusiasm will characterize our acceptance of every new proposed method.

The importance of good diabetic care, in the successful handling of pregnancy in such cases, is emphasized, and he describes the substitutional hormone therapy to prevent toxemia and to promote fetal survival, which, while slowly gaining acceptance, seems still a moot point. The more specific bacterial indications for penicillin or the sulfa drugs in obstetric complications are stated. The prophylactic use of either agent with premature rupture of the membranes or presumably infected labor is, however, not mentioned.

In the discussion of the Rh blood factor in pregnancy, Dr. R. W. Koucky has furnished a very clear and concise résumé of this important problem. In answer to the question, "What type blood should be given to the erythroblastotic baby?" he feels that Rh-negative blood only maintains hemoglobin, whereas a transfusion of Rh-positive blood may divert some of the antibody from the baby's tissues, a desirable conservation.

³*Synopsis of Obstetrics*. By Jennings C. Litzenberg, B.Sc., M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Third Edition, 399 pages with 157 illustrations including 5 in color, The C. V. Mosby Company, St. Louis, 1947.

The incorrect legend for Fig. 140 is still present, as in the first edition. No doubt there will always be a place in any division of medicine for a synopsis as well prepared and as well worth while as this one is for obstetrics.

PHILIP F. WILLIAMS.

In this book, *Rh, Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions*,⁴ Dr. Edith L. Potter, whose unusual experience in the pathology of the fetus and newborn, and fortunate connection with an outstanding maternity hospital have eminently fitted her for the task, has reviewed the extensive literature of the subject and brought it thoroughly digested and logically arranged for our understanding of a very complicated subject.

Dr. Potter opens the discussion with a general survey of the whole problem. Briefly she reviews the discovery of the Rh antibody in rabbits, in recently pregnant women, and the relation of the antibody to transfusion reactions. The survey continues through the characteristics, varieties, inheritances, and racial differences of Rh. The mechanism of immunization is followed by the relation of the Rh to transfusion reactions and to congenital hemolytic disease. The basic principles of determination of Rh character of blood and detection of Rh antibodies are explained.

The importance of the Rh status of the blood to the welfare of a pregnant woman and her infant, both before and after birth, and to anyone who needs a transfusion is emphasized. While one realizes that the continuing literature on the subject keeps the topic in a state of flux, one can also feel that this digest and correlation has missed nothing of note in the material presented to date.

In ensuing chapters Dr. Potter expands on the topics discussed in the general survey. The background of blood grouping, the mechanism of antibodies, the production of immunization and the development of our present blood type system are presented. The theories and studies of intragroup reactions and incompatibility, particularly in the obstetric field, as to toxemia and fetal death, are discussed, together with the research on blood group incompatibilities. Dr. Potter describes the discovery of the Rh factor and the review of transfusion reactions and stillbirths in recent pregnancies from which the evidence of maternal isoimmunization became apparent.

The story of Rh antigens and antibodies is continued as to the physical properties and specific characteristics and the mode of immunization in pregnancy. An interesting paragraph discusses Darrow's postulating correctly the antigenic difference which makes possible maternal sensitization to the fetus, three years before the Rh antibody, a specific antigen, was discovered.

Further in this chapter, Dr. Potter portrays the enlargement of the Rh blood types, illustrated by expanding classifications Wiener offered in 1943, 1944, and 1945, and she clearly explains the complexities of the subtypes which have arisen as further investigative work has proceeded. The inheritance of Rh and Hr by the postulated presence of eight alleles is described and illustrated. The use of various anti-Rh and anti-Hr sera in establishing the possibility of paternity is set forth. In discussing the nomenclature of Rh and Hr, Dr. Potter feels that the plan proposed by Fisher is convenient and equally sound for whatever form of inheritance is finally found to be correct. Certainly a simple uniform nomenclature would help greatly in understanding the publications on the subject. In discussing racial incidence of Rh, she states that where race-crossing is negligible the blood groups probably remain constant for long periods. There is a very clear presentation of the relation of Rh and transfusion reactions. Many practical suggestions are made in this section.

There is an extended discussion of the subject of hemolytic disease, historically, when the cause was unknown and the three varieties appeared to be distinctly different entities, together with the many hypotheses offered in those days, as well as our present understanding

⁴*Rh, Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions*. By Edith L. Potter, M.D., Ph.D., Assistant Professor of Pathology, Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital, 336 pages with 65 illustrations, The Year Book Publishers, Inc., Chicago, 1947.

of the disease with its clear etiological basis. The reason for the rarity of the disease in the first pregnancy is discussed from the standpoint of four main possibilities.

The various clinical contradictions reported, such as hemolytic disease in Rh-negative infants, are discussed and explained. The pathology and clinical course of the disease, diagnosis, complications, and treatment are amply discussed. Dr. Potter does not feel that exsanguination transfusions provide a sufficiently improved outlook for the life of the child to warrant encouraging their use. Postmortem studies and the pathology of the various types of hemolytic disease are thoroughly described.

The final chapter of the book provides discussions for a simple determination of the Rh status of blood cells and the presence of antibodies, as well as the more elaborate technical procedures necessary in differentiating the present varieties of antibodies and antigens. The bibliography lists 794 references to the literature which have been reviewed in the text.

The book is an outstanding résumé and discussion of this all-important subject. The book not only condenses and presents the important papers, but gives as well the experience and knowledge of an interested worker in the field. The book should be of great value to obstetricians, pediatricians, and clinical pathologists, and is highly recommended.

PHILIP F. WILLIAMS.

This small, but thoroughly complete and well-documented volume, *The Premature Baby*,⁵ sums up the fourteen-year-long experience of Dr. Mary Crosse in this particularly important field of medicine in the hospitals and homes of Birmingham, England.

The exigency of the problem lies in the fact that one-half of all deaths of babies in the first month of life are due to their being born prematurely. The description of methods for salvaging prematurely born infants is full and complete; the author is meticulous in describing small but essential details. Together with her own procedures, she adds and describes the successful practices of other workers in the field. The need for well-equipped and staffed premature stations is stressed, and care of prematures from such angles as transport, types of incubators, and prevention of infection is given.

The discussion on the care of the premature under less auspicious circumstances, the home, is full of practical simple suggestions. There is an extensive consideration of feeding, complications, and infection. Over a period of thirteen years Dr. Crosse has achieved the gratifying neonatal mortality rate of but 128 deaths per 1,000 premature live births.

As to the causes of prematurity, in which the readers of this JOURNAL may be more interested, Dr. Crosse rates toxemia of pregnancy, 29 per cent, and multiple pregnancy, 10 per cent, as the most frequent. Unknown etiology was responsible for 38.5 per cent. In two-thirds of this latter group, a history was obtained of two or more previous premature labors or miscarriages. This excellent volume is replete with valuable information for the pediatrician, obstetrician and, premature-station staff.

PHILIP F. WILLIAMS.

Miscellaneous

The importance of cancer as a factor in human mortality makes the appearance of a practical text, such as this volume, *Cancer, Diagnosis, Treatment, and Prognosis*,⁶ by Ackerman and Regato, very timely.

The first five chapters of the book are devoted to subjects of general interest in the whole field of malignant neoplasm. Dr. Michael B. Shimkin, of the staff of the National

⁵*The Premature Baby*. By V. Mary Crosse, M.D. (London). D.P.H., M.M.S.A., D.R.G.O.G., Chief Obstetric Officer in charge of City of Birmingham Maternity Homes and Premature Baby Unit; with Foreword by Leonard G. Parsons, M.D., F.R.C.I., F.R.C.O.G., Professor of Children's Diseases, University of Birmingham; 142 pages with 14 illustrations; The Blakiston Company Philadelphia, 1947.

⁶*Cancer, Diagnosis, Treatment, and Prognosis*. By Lauren V. Ackerman, M.D., Pathologist to the Ellis Fischel State Cancer Hospital; Assistant Professor of Pathology, Washington University School of Medicine, St. Louis, and Juan A. del Regato, M.D., Radiotherapist to the Ellis Fischel State Cancer Hospital; Formerly Assistant to the Radium Institute of the University of Paris; 1075 pages, with 745 text illustrations and 42 color reproductions, The C. V. Mosby Company, St. Louis, 1947.

Cancer Institute, has written an extended and illuminating story of cancer research in which he discusses the role of heredity and the other etiological factors, the characteristics of cancer, the transplantation of tumors and the development of present-day therapies. In discussing the influence of estrogens and other hormones, Shinkin concludes that estrogenic compounds may initiate in some unknown way a number of neoplastic processes, usually of tissues that are normally under the influence of sex hormones.

In the chapter on pathology of cancer, there is a thorough description of the collection and preparation of specimens and the microscopic distinctions, as well as a discussion of the nature of the various growths, their characteristics and methods of extension.

Dr. Bricker, who has edited the chapter on surgery, importantly stresses the need for extensive surgery in extirpating malignant lesions, and concisely discusses the pre- and postoperative care, the selection of anesthesia, and the neurosurgical procedures for relief of pain in advanced cancer. The physical foundation of radio-therapy, the measurement of its quantity and quality, and its biologic effects are discussed generally, followed by practical facts on the clinical use, technical aspects, and limitation of its use as a therapeutic measure.

The remainder of the text is divided according to systems and the particular type of tumor and tissue involved. The discussion of these topics follows the same outline, from anatomy through to prognosis, giving a definite completeness to each presentation.

Malignant conditions of the female pelvic organs form one-sixth of the book. Ovarian tumors are classified, both as to their origin and type, but discussed according to the latter. This section of the book is profusely illustrated with many color plates. The rare types of ovarian tumors are particularly discussed in regard to their ancestry and diagnosis. How extensive an operation is necessary in finding a unilateral ovarian tumor is relatively answered by the authors in an interesting table on the indications for surgical treatment of ovarian tumors.

The important recent literature on carcinoma of the endometrium is amply brought into the discussion of this topic. The authors contrast the American method of hysterectomy when practicable, the use of preoperative radium therapy, and the use of radium in inoperable cases, with Heyman's dissenting opinion that radium alone is the treatment of choice. Considerable space is devoted to the clinical classification of the carcinoma of the cervix. The authors present a series of general rules to aid an examiner in making clinical classifications for fair comparison. Several pages of illustrations are included to bring out the points necessary in making a clinical classification.

Discussing diagnosis, the authors feel that the vaginal smear method cannot compete with the standard methods, such as biopsy of the cervix and dilatation and curettage of the endocervix. In a prophylactic survey of nonsymptomatic women in which biopsy and curettage would not be justified, the examination of vaginal smears may contribute (although at the expense of valuable time and effort) a few early diagnoses of cancer of the uterus.

The evolution of treatment of cancer of the cervix is discussed and the currently used techniques of various clinics are detailed. The authors state, "We believe that thorough external radiation of the pelvis is an important first step in the treatment of all cases of cervical cancer," and again, "If internal radiation can be called the most important single factor in the treatment of early cases, thorough external roentgen therapy is the most important single factor in the treatment of advanced cases." The question of total hysterectomy in nonmalignant lesions is logically regarded by the authors as a question of balance between the greater operative mortality of the radical operation and the incidence of carcinoma in the remaining cervix. There is an excellent discussion of the carcinoma of the cervix in pregnancy and of malignancy of the lower genital tract.

Following the presentation of mammary carcinoma and other remaining systems, the authors give an excellent review of the present opinions on research in, and treatment of, Hodgkin's disease and leukemia.

The excellence and completeness of the presentation and the balance achieved by the dual authorship of a pathologist and a radiotherapist make the text an outstanding contribution on this subject.

PHILIP F. WILLIAMS.

The *Acute Infectious Fevers*,⁷ an introduction for students and practitioners by Dr. Alexander Joe, is divided into fifteen chapters. One concludes, after perusing the book, that the endeavor of the author to answer fundamental questions which are repeatedly asked by students and house officers on the subject has been eminently successful.

The author feels that the result of Dick tests show that women in the puerperium are not more susceptible to scarlet fever than others in the same age group. He does not feel that scarlet fever in childhood predisposes to renal lesions in maturity. The author notes a sensible diminution in the mortality from sepsis in the British Isles, which he attributes to the widespread use of the sulfonamides; he feels an increasing proportion of the sepsis deaths there are due to postabortive sepsis. He recommends the immediate prophylactic use of these drugs after a traumatic labor. The intrauterine instillation of glycerine in sepsis, which he describes, is not a part of the therapy in this country.

The safeguarding of pregnant women, especially during the early months, from contact with rubella cases is emphasized, although no definite statement is offered as to occurrence of congenital defects in the offspring of such affected mothers.

PHILIP F. WILLIAMS.

In the second edition of *Communicable Diseases*,⁸ by Dr. Top and his collaborators, fourteen new chapters have been added. The book is intended as a text and handy reference for all persons whose professional contacts necessitate connection with certain communicable diseases. An excellent chapter in the section of general consideration on the management of communicable diseases in hospitals leaves little to be desired in regard to the care of the patient, not only from the administrative standpoint, but also as to nursing, laboratory procedures, and prevention of cross-infections.

The author has classified communicable and infectious diseases by a common portal of entry, and, further, by the etiological factors as fungi, bacteria, or viruses. Considerable space is devoted to the specific prevention of certain communicable diseases, and there is a chapter on serum and serum reactions.

In discussing German measles and the congenital defects in infants attributed to such infection in early pregnancy of the mother, Top feels it is still too early to assess fully the complications of the reported findings. He feels that the study has been approached from the wrong end, namely, the affected child. He proposes that the pregnant women should be studied in two groups, those who did and those who did not contract German measles during pregnancy, and then the abnormalities in the children of both groups should be noted; differences then might be considered significant. He suggests the use of human immune globulin in the treatment of German measles in early pregnancy, but feels that therapeutic abortion should not be indicated.

In discussing epidemic diarrhea of the newborn, Cummings feels that a filtrable virus is the infectious agent. He discusses the epidemiology of the disease, refers to the lack of significant pathology and to the lack of immunity. He notes that epidemics are more severe when the premature population of a nursery is high, stresses the difficulty of dif-

⁷*The Acute Infectious Fevers, an Introduction for Students and Practitioners.* By Alexander Joe, D.S.C., M.D. (Ed.), F.R.C.P. (Ed.), D.P.H., D.T.M. & H., Medical Superintendent, City Hospital, Edinburgh. Lecturer on Infectious Diseases to the University of Edinburgh. Formerly Medical Superintendent, North-Western Hospital, London. 266 pages with 64 illustrations. The Blakiston Company, Philadelphia, 1947.

⁸*Communicable Diseases.* By Franklin H. Top, A.B., M.D., M.P.H., F.A.C.P. Medical Director, Herman Kiefer Hospital; Clinical Professor of Preventive Medicine and Public Health, Wayne University College of Medicine; Consultant, Preventive Medicine Section, Surgeon General's Office, United States Army, and Collaborators. 948 pages with 95 illustrations and 13 Color Plates. Second Edition, The C. V. Mosby Company, St. Louis, 1947.

ferential diagnosis, and gives an excellent practical schedule for treatment, recommending sulfadiazine. His suggestions for preventability and control state, concisely, a rigid nursery technique.

In discussing chaneroid, Shaffer states that the sulfonamides have revolutionized the treatment of chaneroid, and refers to the 20 per cent sulfathiazole content of the new Army prophylactic. The same contributor, in an excellent discussion of lymphogranuloma venereum, states that the sulfonamides are the most practical method of treatment now available, that the Frei antigen is much less effective. Penicillin, he says, seems to have no effect in this disease.

Granuloma inguinale, according to Shaffer, is uncommon in Detroit, not over twenty cases annually presenting themselves in the Social Hygiene Clinic. He refers to the difficulty in diagnosis, as the type of person affected has often had such previous infections such as syphilis, lymphogranuloma venereum, and chaneroid. Antimony is regarded as the most effective therapy, while penicillin and the sulfonamide group have not been found of value.

Each chapter gives its own bibliography, while an appendix analyzes the communicable diseases seen in the Herman Kiefer Hospital in Detroit over a long period of years. The text is comprehensive from both a curative and a preventive standpoint of the disease discussed, and should be found helpful in many types of practice.

PHILIP F. WILLIAMS.

The lectures to the laity in the March of Medicine Series of the New York Academy of Medicine for 1945 are devoted to *Modern Attitudes in Psychiatry*.⁹ There are six lectures, each by an outstanding authority in the field, which logically and effectively portray the history and development of this branch of medicine, its application to the individual patients, its possible future trends, its usefulness during the recent war, and its application to the recurrent problems of daily practice. To those who may not have realized the important relations of social and environmental problems of the individual patient to his illness, this book is warmly commended.

PHILIP F. WILLIAMS.

⁹*Modern Attitudes in Psychiatry*. The March of Medicine, 1945, 150 pages, Columbia University Press, New York, 1946.

Department of Reviews and Abstracts

Selected Abstracts

Endometriosis

Ahumada, J. C., and Nogues, A. E.: Perforating Fornix Endometriosis, *Obst. y Ginec. Latino-Am.* 4: 651-666, 1946.

The authors have observed 232 women with endometriosis. Among these 12 or 3.4 per cent had endometriosis of the recto-vaginal septum with perforation through the vagina. Brief histories are given of these twelve cases. The symptoms characteristic of perforation of endometriosis of the recto-vaginal septum are as follows: metrorrhagia, premenstrual and intramenstrual pain sometimes associated with rectal pain, and infiltration of the vagina by the tumor resulting in folds and wrinkles in the vagina. Often hemorrhagic cysts are observed and a later development are soft polypoid structures presenting a dark, bluish red tint.

There are three pathologic types: (1) the primary type, (2) the type which is secondary to continuous growth from the adnexa and (3) the type which results from endometriosis of the uterus.

The treatment of choice is surgical, being conservative in women under 40 and radical after this age. If there is a contraindication to surgery, roentgen therapy should be used. Radium is not beneficial. The prognosis is good. All the patients in this series were cured.

J. P. GREENHILL.

Gynecology

Alfieri, P.: Angioma of the Vulva, *Clin. obstet.* 48: 145, 1946.

Angioma of the vulva is an uncommon finding. Alfieri thoroughly reviews the literature on the subject and describes a case of cavernous angioma of the vulva in which both labius majus and the clitoris were involved, a quite unique localization previously noted only by Taussig.

The tumor was present at birth, however, had been growing progressively since, and its histologic features readily differentiate it from a congenital anomaly (amathoma) so often classified as, and confused with, blood vascular tumors.

The angioma appeared mainly composed of large venous cavities lined with vascular endothelium, containing blood in large quantities. A negligible amount of fibrous stroma was present. At the periphery, the growth appeared made up of capillaries with a minimal amount of supporting stroma. No other tissue was present, nor was more significant parvicellular infiltration seen.

The patient was cured by surgical ablation of the tumor.

GEMMA BARZILAI.

De Giorgi, L.: Sudoriferous Gland Tumor on the Labia, *Arch. di ostet. e ginec.* 51: 119, 1946.

De Giorgi reviews the continental literature on the subject and describes a case of sudoriferous gland adenoma of the labia. The tumor was boggy on palpation and micropictures presented, as well as the microscopic description, correspond to features of what in this country is called hydradenoma papilliferum. The growth was well encapsulated and made up of cystic and papillary portions. The epithelium appeared arranged in two layers, one corresponding to the secretory lining of sudoriferous glands, the other to the outer myoepithelial layer.

GEMMA BARZILAI.

Calmenson, Marvin, Dockerty, Malcolm B., and Bianco, John J.: Certain Pelvic Tumors Associated With Ascites and Hydrothorax, *Surg., Gynec. & Obst.* 84: 181, 1947.

Nine instances of a pelvic tumor associated with ascites were found in approximately 20,000 records of pelvic tumors. These cases are reported in detail. The ovarian tumors were all large, averaging 16 cm. in diameter and included five ovarian fibromas, one degenerating uterine fibromyoma, one fibromyoma of the uterus with pelvic inflammatory disease, one granulosa cell tumor and one teratoma of the ovary. The major contribution of the paper is the suggestion that the development of the ascites is related to the edema and large size of these tumors. To substantiate this it was noted that fifty-one tumors which were accompanied by ascites showed edema in 96 per cent while only 10 per cent of tumors unaccompanied by ascites showed edema. The theory for development of hydrothorax is discussed but no conclusive proof as to the origin of this fluid is offered.

M. HELLMAN.

Gynecologic Operations

da Silva Loureiro, O.: Vaginal Hysterectomy for Nonmalignant Conditions of the Uterus, *An. brasil de ginec.* 22: 276-281, 1946.

At the Gynecologic clinic of the Brazil National Faculty of Medicine, 57 vaginal hysterectomies were performed for nonmalignant conditions of the uterus. The principal indications were prolapse of the uterus with cervical erosion, 30; interstitial fibromyoma of the uterus, 13; and glandular hyperplasia of the uterus with metrorrhagia, 9. There were no deaths in this series. The ages of the patients varied from 41 to 74 years. The Mayo-Kelly operation was used in the prolapse cases, and the Martius technique was employed in the other cases. Local anesthesia was used in all of the cases.

J. P. GREENHILL.

de Aquino Salles, A., and Conri, A. A.: Bilateral, Simultaneous Uretero-Entero Anastomosis According to the Davalos Technic in the Treatment of Incurable Vesicovaginal Fistulas, *An. brasil de ginec.* 22: 263-275, 1946.

The authors report two cases of incurable vesicovaginal fistula treated by bilateral simultaneous ureterointestinal implantation according to the Davalos technique. These may be the first cases in which the operation was performed on human beings. The operation is simple and does not interfere with the flow of urine. The use of sulfonasydine helped considerably. Transient anuria was present until the third day but subsided spontaneously. Intravenous urographic studies showed that hydroureters developed after operation but that progressive improvement followed this occurrence.

J. P. GREENHILL.

Labor

Hansen, Jens L.: Spinal Anesthesia as Therapy in Cases of Postpartum Uterine Atony, *Acta obst. et gynec. Scandinav.* 22: 1943.

Hansen proposes the use of low spinal anesthesia in cases of postpartum hemorrhage caused by uterine relaxation, based on his experience with four cases. He feels that a spinal should be given after "the usual extragenital measures" (oxytocic and uterine massage) have failed. The reaction of the individual reader to the author's suggestion that spinal anesthesia be used before such comparatively simple measures as uterine packing are tried is unimportant as compared to the clarity with which Hansen emphasizes the fact that any postpartum bleeding in excess of 500 c.c. is serious and calls for immediate action. He urges that every accoucheur must have planned beforehand just how he will cope with every case of postpartum hemorrhage. He must know how much time will be allowed to elapse and how much blood lost before a more active step is taken. Naturally, blood transfusion is the most important of all these steps.

HERBERT J. SIMON.

Tonkes, E.: Rupture of the Membranes Before the Onset of Labor, *Gynaecologia* 123: 58-72, 1947.

Tonkes, of Middelburg, Holland, reviews the infant mortality of his country and compares it to other continental countries as an introduction to his article. These figures are significant. During the years 1924 to 1939, there were 2,675,018 deliveries in Holland with 68,137 stillbirths; an incidence of 2.547 per cent. This percentage was compared to The Hague statistics for the near period of 1929 to 1936, and revealed the stillborn percentage for Germany was 2.83; Belgium, 3.24; England, 4.07; Australia, 2.77; France, 3.35; and Switzerland, 2.26 per cent.

In the effort to improve the fine Dutch figure, the author considers the role of premature rupture of the membranes and its possible relationship to stillbirths. In his opinion, this procedure is dangerous, and is the cause of increase in infant mortality. To support his impressions Tonkes collected sixty-six cases. In this group occurred two maternal deaths, seventeen stillbirths, three cases of neonatal cerebral hemorrhage and one case of imbecility. He emphasizes that to overcome uterine atony often seen with premature rupture of the bag of waters pituitrin is indicated in mothers with normal pelvis to accelerate labor prior to the end of the second stage. In cases with borderline bony parts vaginal cesarean section is indicated, according to Tonkes.

C. E. FOLOSOME.

Amorin, J., Lacreta, O., and Endrizzi, L.: Pregnancy and Labor in the Presence of Excessively Large Babies, *An. brasil de ginec.* 22: 393-401, 1946.

The authors reviewed the records of 3,173 pregnant women and found that 120 had given birth to babies which weighed more than 4 kg. (8.8 pounds). This is an incidence of 3.7 per cent. More than one-half of the mothers of the 120 babies were between 25 and 35 years of age, and the following complications were associated with the gestation: malaria, 12 per cent; syphilis, 5 per cent; heart disease, 0.83 per cent; and hyperthyroidism, 0.83 per cent. Hypertension was present in 20 per cent, and in 19 per cent the pregnancy went beyond three hundred days. The membranes ruptured spontaneously in 76 per cent of the cases. Dilatation of the cervix required more than twelve hours in 41 per cent. Labor was normal in 82.5 per cent. Operative deliveries were as follows: forceps, 8.53 per cent; cesarean section, 0.83 per cent; Zaraté symphysiotomy, 0.83 per cent; external version, 0.83 per cent; and embryotomy, 1.66 per cent. Among the mothers there was one case of shock, perineal laceration in 7.5 per cent, and vaginal cervical lacerations in 3.33 per cent.

In 10 per cent of the cases bleeding was excessive. Fetal asphyxia occurred in 10.83 per cent, and the incidence of fetal death was 4.16 per cent. The puerperium was normal in 75 per cent.

J. P. GREENHILL.

Heffernan, Roy J., and Sullivan, Charles Leavitt: Complete Absence of Lochia Following Delivery. *New England J. Med.* 236: 65, 1947.

The case of a 40-year-old primigravida delivered by cesarean section four weeks before term is presented by the authors. Vulva pads were carefully inspected, and remained perfectly dry during her entire convalescence. On the twenty-first day following delivery, menstrual flow began.

Two possible explanations are given.

JAMES P. MARR.

Barnes, Josephine: Pethidine in Labor: Results in 500 Cases, *Brit. M. J.* 4500: 437-442, 1947.

Pethidine is an English proprietary name for 1-methyl-4-phenyl-peperidine-4-carboxylic acid ethyl ester hydrochloride. It is known as "dolantal" in Germany, as "dolantin" in South America and as "demerol" in the U. S. A. and Canada, where it was also termed S-140 and D-140. Actually the drug was introduced as a synthetic substitute for atropine.

Barnes reviewed the results following use of pethidine in labor among 500 patients, 479 primigravidas and 21 multiparas on the Obstetric Unit of the University College Hospital. There was no maternal mortality. Eleven mothers noted slight toxic symptoms—characterized by dizziness, or feeling of faintness, giddiness or numbness, sweating, and slight retching. The effects were said to be transient.

The fetal mortality was sixteen stillbirths, 3.2 per cent, and five neonatal deaths, 1.0 per cent. Signs of asphyxia were noted in fifty-five infants, 11.0 per cent; recovery occurred in all. Pethidine may have contributed to slight respiratory depression in a few cases.

Good analgesia was experienced by 55.0 per cent of mothers. Perhaps in some failure the drug may have been given too late. Amnesia was obtained in only 10.0 per cent. Some symptomatic relief was experienced by 87.0 per cent of the cases. No effect on uterine contractions was noted in 67.0 per cent. In 23.3 per cent contractions appeared to increase, while in 8.7 per cent they seemed to decrease.

The duration of labor was compared in primigravidas with a control series of patients delivered in 1939. It was found that the first stage was seven hours longer in patients receiving pethidine ("demerol"). The claim that pethidine shortened labor could not be substantiated.

The forceps rate was 9.2 per cent, as compared to 7.8 per cent in the control series of 1939. No tendency to postpartum hemorrhage was observed. Pethidine was given as premedication for cesarean section in 32 cases. Although this drug did not fulfill all the Sturrock criteria as an ideal analgesia, it seemed to approach this ideal more nearly than any other obstetric analgesic in current use.

C. E. FOLSOME.

Miscellaneous

Hattersley, Lt. Paul G.: Two Popular Fallacies Regarding Rh, *J. Lab. & Clin. Med.* 32: 423, 1947.

The author presents data to correct two fallacious Rh beliefs which he fears are widespread:

(a) The belief that sensitization of Rh-negative persons by Rh-positive blood transfusion is infrequent; in his group blocking Rh antibodies were demonstrated in 55 per cent by the use of albumin-suspended cells.

(b) The belief that blocking antibodies are always of Rh₀ specificity; by the use of the albumin-suspended cell technique he demonstrated Rh' antibodies in 60 per cent and RH" antibodies in 15 per cent of his apparently nonreacting (saline-suspension) sensitized group.

This work emphasizes the importance of properly prepared sera.

S. B. GUSBERG.

Perez, M. L., and Echevarria, R.: Prophylactic Intraperitoneal Sulfonamide Therapy in Obstetric Surgery and in Impure Cases, *Obst. y Ginec. Latino-Am.* 4: 447-552, 1946.

The authors reviewed the literature and studied their own obstetric cases where the sulfonamides were used as a prophylactic measure. In a series of more than 700 cases, the mortality in the group which received sulfonamides prophylactically was 0.81 per cent as contrasted with a death rate of 4.3 per cent for the group which were not given the sulfonamides. Among the 613 patients who had had transperitoneal cesarean sections and were given the sulfonamides prophylactically, the maternal mortality was 0.32 per cent. This is considerably below the incidence of 3.33 per cent which is the mortality rate usually quoted for extraperitoneal cesarean sections.

The authors' choice of cesarean section is the Opitz transperitoneal type. There were no deaths from peritonitis. In their last twenty-eight cases of unclean cases the authors added penicillin therapy to the intraperitoneal sulfonamide treatment and the results were so strikingly good that they believe the problem of cesarean section in impure cases has been solved.

J. P. GREENHILL.

Puerperium

Wassenaar, J. J. S.: Postpartum Intra-abdominal Separation of Uterus, *Brit. M. J.* 4500: 452, 1947.

The patient, a 25-year-old primipara, purportedly gave birth to a male infant, in her home, after a labor of eight and one-half hours. The attending nurse could not expel the placenta by simple means. A physician was called. He administered two doses of ergometrine and one dose of calcium gluconate. Seven hours after delivery the patient was admitted, in shock, to the Germiston Hospital. After control of shock, a twenty-five-minute attempt to manually remove the placenta revealed omentum. The author was called and, concurrent with more anti-shock treatment, a laparotomy was done.

The uterus was found completely severed, and only three relatively small bleeding points seen. The stretched cervix was torn through and severed from the body of the uterus; the Fallopian tubes were torn off separately; the ovaries were intact. There was no damage to ureters or adjacent visceral organs. The uterine arteries could not be found. The patient, with use of postoperative sulfadiazine and penicillin, left the hospital on the seventeenth day. Examination of the specimen revealed long pieces of uterine arteries attached to the specimen, apparently torn off at their origins from the internal iliac arteries.

The author concludes by asking numerous questions without attempting to answer them, for whatever the answer, this case, in his opinion, was without parallel in view of the severity of the lesion and the survival of the patient.

C. E. FOLSONE.

Barnes, Allen C.: Postpartum Blood: Its Clotting Mechanism and Relationship to the Peripheral Blood Picture, *Am. J. M. Sc.* 213: 463-469, 1947.

Barnes, Ohio State University Medical School, restudied the "coagulation defect" of postpartum uterine blood. This blood fraction does not clot in vitro spontaneously or on the addition of the following substances singly: calcium, thromboplastin, trypsin, fibrinogen or thrombin. Therefore, it does not resemble oxalated, citrated or heparinized bloods, or recalcified plasma. Postpartum blood will clot upon the addition in excess of a mixture of thrombo-

plastin and fibrinogen, or on "seeding" with small amounts of freshly drawn venous blood. It displays a clot promoting action and a definite, but weak, proteolytic activity. Thus it behaves in a manner similar to defibrinated blood or a suspension of cells in serum.

The hematologic and chemical characteristics of postpartum uterine blood were investigated. Its cell count varied daily during the puerperium. This variation gave a characteristic pattern, with a steady fall in the hemoglobin and red cell count and a rapid rise in the white cell elements.

Variations in the clotting mechanism of the peripheral blood on the amount of postpartum blood loss were measured. Prolongation of the prothrombin and clotting times (by dicumarol and heparin) did not decrease the amount of postpartum blood lost. The administration of vitamin K was without effect in raising the (already elevated) prothrombin level of the patient immediately postpartum, and was without effect in diminishing vaginal blood loss.

Barnes states that the most important single factor influencing the amount of blood loss following delivery is the mechanical closing of the sinuses in the placental bed, which is dependent upon the efficiency of the uterine contraction and unrelated to the coagulation tendencies in the circulating blood. Therefore, no definite relationship could be established between the peripheral blood coagulability and the amount of postpartum bleeding.

C. E. FOLSOME.

Toxemia

Krieger, Vera I., and Weiden, Sara: The Value of the Cold Pressor Test in the Prediction of Hypertension and Toxemia in Pregnancy, *M. J. Australia* 1: 417-423, 1947.

The authors, of the Department of Pathology, Women's Hospital, Melbourne, re-evaluate the cold pressor test of Hines and Brown. In a series of 522 cold pressor tests performed during 200 pregnancies, all tests gave normal results in eighty-four instances, hyperaction to the cold stimulus occurred in one test only on each of thirty-one patients and in more than one test on each of eighty-five patients. Only thirteen of the patients, all of whose cold pressor tests gave normal results, developed hypertension in the latter part of their pregnancies. Four of this group developed pre-eclampsia.

In a group of 506 patients in which no cold pressor tests were made during pregnancy, basal blood pressure readings and cold pressor tests were made two months after the completion of pregnancy. In 12 per cent of these normal cases there was an abnormal response, but this figure increased to 36 per cent when the patients had had mild toxemia. After pre-eclampsia more than 50 per cent gave hypertensive evidence.

The writers concluded the results of the cold pressor tests during pregnancy were of value to the obstetrician, since, even if only one response in the series was of the hyperactive type, 50 per cent of the cases giving such responses developed hypertensive or preclamptic toxemia. When two or more abnormal results were obtained, the number of patients who developed toxemia increased to nearly 70 per cent. On the other hand, toxemia which occurs late in pregnancy in only a few cases in which the response to the test was always normal.

C. E. FOLSOME.

Smith, George Van S., and Smith, O. Watkins: Late Pregnancy Toxemia, *West. J. Surg.* 55: 288, 1947.

The late toxemias of pregnancy are the result of escape from the uterus into the general circulation of a toxic protein, resulting from tissue breakdown in the endometrium, as a result of premature withdrawal of estrogen and progesterone. The normal conversion of estradiol to estrone and estriol is facilitated by progesterone. Premature labor, intrauterine death, pre-eclampsia and eclampsia are associated with a premature drop in progesterone, which results in an incomplete conversion of estradiol, which is followed by tissue catabolism and

a release of toxin. The premature aging of the toxemic placenta collaborates and is a part of the events described above. The toxin liberated from the endometrium after premature estrogen and progesterone withdrawal is similar to the menstrual toxin resulting from tissue break-down in the normal menstrual cycle. The elevation of chorionic gonadotropin results from the failure of the aging syncytium to perform its normal function of utilizing it in the production of estrogen and progesterone. It is concluded that late toxemias of pregnancy are the result of a tissue toxin which results from tissue necrosis in the decidua following premature withdrawal of estrogen and progesterone.

WILLIAM BICKERS.

Brouse, L. T.: Hemorrhage Following Toxemia, *Obst. y Ginec. Latino-Am.* 4: 749-762, 1946.

The author maintains that in the presence of toxemia, with its associated edema, the uterine musculature undergoes changes which result in dissociation of the fibers. The uterus therefore becomes atonic, and there is inertia during labor. During the third stage the inertia may result in hemorrhage, with consequent severe anemia and even death. At the El Salvador Maternity the mortality from the inertia and hemorrhage which result from toxemia was 10.1 per cent. The author believes that the association of toxemia and uterine inertia with hemorrhage is much more frequent than is generally admitted. There is no relationship between the severity of the toxemia and the degree of atony of the uterus or amount of bleeding. The author favors expectant and conservative therapy for toxemia chiefly in the form of sedation, blood transfusion and medical induction of labor by the method of Kreis.

J. P. GREENHILL.

Venereal Disease

Becker, S. William: Practical Aspects of Verification Tests for Syphilis in Office Practice, *Am. J. Syph. Gonorr. & Ven. Dis.* 31: 225, 1947.

The author concludes that on the basis of a small series of cases, the Kahn verification procedures seem to support the multiple diagnostic attack of Stokes in evaluation of positive blood tests as seen in private syphilologic practice. They are not recommended for the nonsyphilologist.

The use of cardiolipin and purified lecithin (Pangborn) and use of newer chemical methods devised by Neurath promise to be of even greater assistance in identification of nonspecific positive blood tests.

C. O. MALAND.

Callaway, J. Lamar: The Weltmann Serum Coagulation Reaction in Syphilis, *Am. J. Syph. Gonorr. & Ven. Dis.* 31: 216, 1947.

The author summarizes the article as follows: (1) The results of the Weltmann serum coagulation reaction in 610 patients with syphilis are given. (2) With the exception of thirty-four patients with prenatal syphilis, the Weltmann coagulation reaction band was either normal or revealed a tendency toward moderate but distinct shift to the right with a prolongation of the coagulation band. (3) Thirty-two patients with early syphilis received six months' treatment with an arsenical and bismuth, without appreciable change in the Weltmann coagulation band. (4) Fever therapy and penicillin therapy in patients with syphilis of the central nervous system exerted no specific effect on the Weltmann coagulation reaction band. (5) Sex or race seemed to exert no effect on the Weltmann reaction band in this study.

C. O. MALAND.

Correspondence

Pulmonary Embolism From Amniotic Fluid

To the Editor:

In the December, 1947, issue of the *JOURNAL*, Drs. Leo Seltzer and William Schuman¹ reported a possible case of nonfatal pulmonary embolism by amniotic fluid contents. The authors described a syndrome of cyanosis, dyspnea, tachycardia, shock, and pulmonary edema occurring during delivery under general anesthesia. X-rays revealed bilateral areas of increased density without atelectasis or mediastinal shift. These areas cleared approximately ninety-six hours later. The authors also considered the possibility of aspiration of gastric contents but discounted this because of the absence of any recognizable anesthetic difficulties and the absence of atelectasis in the roentgen findings.

The aspiration of gastric contents during obstetric anesthesia can produce two entirely different syndromes.² There may be gastric retention of solid or liquid material during labor. The aspiration of solid food usually produces laryngeal or bronchial obstruction. Complete obstruction produces suffocation. Incomplete obstruction produces massive atelectasis with the classical picture of cyanosis, tachycardia, shock, dyspnea, mediastinal shift, and signs of consolidation over the collapsed area. X-rays reveal a homogeneous density and varying degrees of mediastinal shift. The pathology and treatment of atelectasis are well recognized.

The aspiration of liquid material produces a syndrome with distinct clinical, roentgenologic, pathologic, and therapeutic features. This syndrome had apparently escaped previous recognition. There is cyanosis, tachycardia, dyspnea, and shock, but no massive atelectasis or mediastinal shift. Wheezes, râles, and rhonchi are heard over the affected portions of the lungs. X-rays reveal irregular, soft, mottled densities without mediastinal shift. The picture has been confused with pulmonary embolism, bronchopneumonia, tuberculosis, fungus infection, and even metastasis. Progressive cardiac failure and pulmonary edema may supervene, regardless of the previously normal condition of the heart. Here the diagnosis has been confused with primary heart failure. Experimental work indicated that gastric hydrochloric acid produces a bronchiolar spasm and a peribronchiolar congestive and exudative reaction interfering with normal intrapulmonary circulation. Therapy should be directed against the bronchiolar spasm and cardiac embarrassment. Oxygen, atropine, adrenaline, and aminophylline will accomplish these objectives. Rapid intravenous digitalization is indicated in the event of cardiac decompensation. Bloodless tourniquet phlebotomy will further relieve the circulatory burden. Stellate ganglion block was also suggested. The bronchoscope would appear to be of little value for the pathologic process is beyond reach, and endoscopy may only increase the existent spasm and dangers of secondary infection. The majority of patients have an afebrile recovery with complete clearing of the chest in seven to ten days. The pathologic process is primarily irritative and not infectious but prophylactic use of chemotherapy or antibiotics may be of value. This type of aspiration may be prevented by withholding all oral feeding during labor and substituting parenteral routes where necessary. Alkalinization of, and emptying the stomach contents prior to the administration of a general anesthetic was also suggested among other prophylactic measures.

The case reported by Drs. Seltzer and Schuman also suggests that their patient could have aspirated liquid gastric contents. The clinical, roentgenologic, and therapeutic features support this diagnosis. It is not surprising that the actual aspiration could have gone unrecognized, for in the study² referred to, it was undetected in 32 per cent of cases. I have questioned the diagnosis of embolism of amniotic fluid contents to draw attention to the

liquid aspiration syndrome, since the latter probably occurs more frequently and is preventable. Although the authors have not been didactic about their diagnosis, they have apparently overlooked another explanation for their findings.

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1. Seltzer, L. M., and Schuman, W.: AM. J. OBST. & GYNEC. 54: 1038, 1947.
2. Mendelson, C. L.: AM. J. OBST. & GYNEC. 52: 191, 1946.

CURTIS L. MENDELSON, M.D.

NEW YORK, N. Y.
January 18, 1948.

Reply by Drs. Seltzer and Schuman

To the Editor:

In reply to the letter by Dr. Mendelson concerning his comments on the diagnosis of the case reported by us,¹ we wish to state at the outset that the diagnosis of aspiration of stomach contents was not "overlooked," as stated by Dr. Mendelson. In our discussion of "Differential Diagnosis" under item No. 4, "Aspiration of Blood or Stomach Contents," we specifically discussed that possibility. In deference to Dr. Mendelson's fine contribution to our knowledge of the pathologic physiology of the effects of aspiration of stomach contents, of which we were aware at the time we wrote our article, we could not omit the possibility of that syndrome.

There is no question that the clinical syndrome described by Dr. Mendelson² AND Drs. Steiner and Lushbaugh^{3, 4} have great similarity. However, from the point of view of mode of onset, there is great disparity. Dr. Mendelson's original paper describes an "Asthmatic-Like Syndrome" which he ascribes to the irritative effect on the bronchial tree of aspirated hydrochloric acid in the stomach contents. One would assume that this would produce a severe cough following restoration of reflexes after the obtunding effect of a general anesthesia has worn off. One patient did not cough until 11 hours following the cessation of anesthesia (productive of frothy, pink sputum) and coughing is not mentioned in a single fatal case reported by Steiner and Lushbaugh,^{3, 4} Hemmings,⁵ and Gross and Benz.⁶ It is our impression that clinically coughing would constitute a very important differential diagnostic criterion. In pulmonary embolization, the severe shock (which our patient demonstrated initially) is most striking, with cough developing subsequently, as the effect of the pathology produced by the embolism increases.

Further evidence to enforce our diagnosis are the following facts of our case:

1. The patient ate her last full meal the evening before admission (fourteen hours).
2. She had only a cup of coffee for breakfast one hour before she was admitted, not in labor.
3. No solid food was given during her labor and only a bowl (approximately 200 c.c.) of broth was given per os during her labor of 11 hours and 12 minutes.
4. There was no evidence of vomiting throughout her labor and she was rather closely observed by the house-staff physicians and nurses during this period because of "breech" presentation.
5. There was no coughing, retching, or vomiting during the induction of the anesthesia and none during or following the delivery. Aspiration produced no fluid or particulate food when the patient went into the profound state of shock described.
6. According to the statement of the anesthetist (one of the full-time anesthesia staff) the induction was very smooth and the amount of anesthesia required was minimal. This has been verified several times.

In spite of the well-known fact of delayed emptying time of the stomach during labor, it hardly seems likely that our patient had sufficient solid particulate food in her stomach, that might have been aspirated, to produce the syndrome we described. Dr. Mendelson points out very significantly that, in 32 per cent of the cases at the New York Hospital,

aspiration of stomach contents was unrecognized, and this may also be true in our case. However in view of the history and findings this possibility seems remote.

Finally, and we become repetitious, aspiration of stomach contents would not give the roentgenologic evidence of bilateral pulmonary infarction which our patient presented.

As this discussion indicates, as yet an absolute diagnosis of pulmonary amniotic fluid content embolism cannot be made in the living patient. Gross and Benz⁶ suggest an excellent blood sediment technique worked out on postmortem cases, in which three definite layers of material, the uppermost being particulate amniotic fluid material, appear in cases of pulmonary embolism by amniotic fluid. However, as they state, the blood must come from the right side of the heart or inferior vena cava, which limits its clinical feasibility prior to demise.

In closing, we wish to thank Dr. Mendelson for his interest in our paper, and the editor for the opportunity of answering Dr. Mendelson in this column.

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2. Mendelson, Curtis L.: AM. J. OBST. & GYNEC. 52: 191, 1946.
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LEO M. SELTZER, M.D.

WILLIAM SCHUMAN, M.D.

BALTIMORE, MARYLAND.

FEBRUARY 7, 1948.

Cornification in the Cervix and Estrogenic Activity

To the Editor:

Recently an interesting study by Ayre (Ayre, J. E.: AM. J. OBST. & GYNEC. 54: 363-389, 1947) has appeared. In it, he hypothesizes an ingenious theory of the possible causation of cervical carcinoma, stressing three factors: chronic inflammation, dietary deficiency, and estrogenic activity. It is concerning the last of these factors that some discussion seems in order.

Ayre states, "The vaginal cornification count provides a simple method of obtaining a reasonably accurate estimation of endogenous tissue estrogens . . ." Later he observes, "the cervical cornification counts were found to be almost consistently higher than the vaginal cornification counts in the same cases." Thus, in 87 per cent of 125 cases studied "without regard to disease," he noted higher cornification in the cervical than in the vaginal smear.

Cornification in the smear is not always the result of estrogen stimulation. Papanicolaou has noted it frequently in chronic inflammatory processes of the cervix or the vagina. Intercourse may produce it; it is increased in cases of threatened abortion. Infection with the *Trichomonas vaginalis* often produces a very high cornification—at times even after the cessation of menstruation.

In many instances of cervical malignancy, there is an associated cervicitis due to secondary infection, and a surprising number of these women have a trichomonas infestation. It may therefore be argued that the cornification in such cases is due to the infection rather than to the carcinoma.

Greene and Peckham (Greene, R. R., and Peckham, B. M.: AM. J. OBST. & GYNEC. 54: 611-616, 1947) also question the validity of using the vaginal smear alone as a quantitative index of endogenous estrogen production. They point out that cornified smears may be found in postmenopausal women.

Finally, if one takes a cervical smear by scraping the surface, he will obtain a correspondingly higher per cent of cornified cells, since these cells are located in the more superficial layers of the stratified squamous epithelium. Conversely, the vaginal fluid serves to dilute the concentration of cells, and these cells represent a desquamation from all layers of the vaginal and cervical mucous membranes. It appears obvious that cervical smears taken by scraping will usually contain more cornified cells than vaginal smears taken with a pipette.

These considerations do not detract from the interest which Ayre's contribution should arouse. It is merely felt that his contention that cornification is an index of endogenous estrogenic activity may possibly be modified by some of the factors mentioned.

LOCKE L. MACKENZIE, M.D.

471 PARK AVENUE
NEW YORK CITY.
Jan. 21, 1948.

Reply by Dr. Ayre

To the Editor:

Dr. Mackenzie's interesting remarks provoke further discussion relating to cornification and estrogenic activity.

He states, "Cornification in the smear is not always the result of estrogen stimulation. Papanicolaou has noted it frequently in chronic inflammatory processes of the cervix or the vagina. Intercourse may produce it; it is increased in cases of threatened abortion. Infestation with the *Trichomonas vaginalis* often produces a very high cornification—at times even after the cessation of menstruation." We, too, have observed increased cornification in smears in chronic inflammatory processes. The question arises: Does this argue against the proposed theory of concentration of estrogen in inflamed or in irritated tissues or does it strengthen the concept? It would seem logical that the "repair hormone" might be concentrated as a defense mechanism at the point of injury or damage.

There are many things that we do not know about cornification and estrogen metabolism. In intercourse, may you not have an increased exfoliation of surface cornified cells to account for the apparent rise in cornification? In cases of threatened abortion we, too, have observed the rise in cornification. Is this not due to a fall in the antagonistic luteal hormone rather than a quantitative increase in estrogen?

It is perhaps important to differentiate, too, between pseudocornification, which is an acidophilic-staining cell with a large immature nucleus, and true cornification, which is the mature end product of pure growth stimulation, a morphologic interpretation of a cell with a small, mature, cornified nucleus. The nuclear morphology is of greater significance than the acidophilia.

In our experience, the acute or subacute stage of inflammation is associated with some increase in true cornification, but a greater proportion of acidophilic cells which are pseudocornified. This is the picture we have found in patients with primary trichomonas infestation, e.g., even in virgins without signs of other disease. Our contention has been that the chronic inflammation has been perhaps the primary factor focalizing the area of proliferation. Then the concentration of the cornification in this region of proliferation has been secondary to the inflammatory state. While we cannot be dogmatic as to which was first in the cervix, the inflammation or the cancer, a certain amount of our evidence suggests that the inflammation preceded the malignant change.

The evidence for the concentrations of estrogen found in the cervix is the finding of cornified cells concentrated in the normal squamous epithelium encircling the squamo-columnar junction. Therefore, in the preclinical cancer, in the cervix which looks normal, yet harbors an early cancer, the same scraping with the spatula which reveals the unexpected cancer cells scrapes also the adjacent normal-appearing squamous epithelium. In this epithelium is found the concentration of cornified cells. On the other hand, in the presence of a large ulcerating

clinical cancer, obviously, smears or scrapings from the cervical opening would yield only cancer cells, blood, and secretion. It would be necessary to scrape the squamous epithelium adjacent to the growth to obtain the cornification index in this tissue.

While the vaginal smear, or better, the selective scraping method, as a quantitative index of endogenous estrogen, is far from ideal, what better method do we have available today? The cell method seems to be superior to proliferative activity as measured by endometrial biopsies. The fact that cornified smears may be found in a small number of postmenopausal cases does not indicate that this is a normal finding. May it not be that this small group of women who show this, do possess some disorder of estrogen metabolism which may possibly endanger them to some of the influences which may ultimately produce a carcinoma?

We are in agreement with Doctor Mackenzie's arguments regarding the method of obtaining smears. The vaginal fluid, undoubtedly, serves to dilute the concentration of cells. However, when a vaginal aspiration was compared to a cervical external os aspiration in early cancers (in which the squamous epithelium of the junction remained close to the cervical os), the higher concentration of cornified cells was usually found in the cervical smear. Comparative scrapings in the same patients from the cervix and from the vaginal wall confirmed the higher concentration of cornified cells in the cervical epithelium. Obviously, smears must be compared only to smears, and scrapings to similar scrapings from a different area.

J. ERNEST AYRE, M.D.

MONTREAL, QUEBEC.

Feb. 14, 1948.

Endometriosis and Estrogen Therapy

To the Editor:

Endometriosis and adenomyosis are now being reported by careful gynecologic surgeons and pathologists in one out of five pelves. Many of those reported are symptomless, but fairly regularly the diagnosis is made and conservative surgery used as therapeutics. Numbers of these patients then are seen by other medical men, who do not understand, or fail to take cognizance of, the implications of the diagnosis of endometriosis. These patients are subsequently placed on estrogen therapy. This therapy in turn can be in the form of minimal doses which seem not to stimulate the endometriosis very much, but I have seen numerous patients who have had large doses of estrogen and who have had marked reactivation of their endometrial symptoms.

I should suggest that, whenever a diagnosis of endometriosis is proved, either at the operating table or in the pathologic laboratory, the patient be instructed that she is never to have estrogenic therapy for any reason whatsoever, unless full cognizance is taken of the possibility of recurrence of the remaining endometriosis and the possible results of such therapy.

LOWELL F. BUSHNELL, M.D.

LOS ANGELES, CALIF.

March 10, 1948.

Necrology

FREDERICK W. RICE, M.D., obstetrician and gynecologist of New York City, died there on March 30, 1948, at the age of 68. He was a graduate of the College of Physicians and Surgeons in 1906, and served as surgeon with the rank of Captain in the first World War. He was an attending obstetrician at Bellevue Hospital, Professor of Obstetrics at the New York University College of Medicine until his retirement in 1934, consulting obstetrician in several hospitals, Fellow of the New York Obstetrical Society and the American College of Surgeons, a Diplomate of the American Board, and active as a Roman Catholic layman in the New York Archdiocese.

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathology examinations (Part II) for all candidates will be conducted at Washington, D. C., by the entire Board from Sunday, May 16, through Saturday, May 22, 1948. The Shoreham Hotel in Washington will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Shoreham.

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1, 1948.

Candidates in military or naval service are requested to keep the Secretary's office informed of any change in address.

Applications are now being received for the 1949 examinations. For further information and application blanks, address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

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Original Communications

NORMAL AND CYSTIC STRUCTURES OF THE BROAD LIGAMENT*†

GEORGE H. GARDNER, M.D., R. R. GREENE, M.D., AND B. M. PECKHAM, M. D.,
CHICAGO, ILL.

(From the Obstetrical and Gynecological Service at Wesley Memorial Hospital and the Department of Obstetrics and Gynecology at Northwestern University Medical School)

THE literature on broad ligament cysts was reviewed in an attempt to find or to formulate an accurate classification of these structures. The results were unexpectedly confusing. The terminology used by various authors was highly individualistic. The following names were noted: paratubal cyst, parovarian (also para-ovarian, parovarial) cyst, Wolffian cyst, intraligamentous cyst, Kobelt's cyst, epoophoral cyst, fimbrial cyst, junctional cyst. The remnants of the embryonic mesonephros (Wolffian body), from which most authors believe these cysts to be derived, were called variously: Wolffian body, epoophoron, Organ of Rosenmüller, Kobelt's tubules, parovarium, parovarial tubules. Anatomical descriptions, particularly as to histology, were equally varied. Opinions on histogenesis were less diverse but were frequently beclouded by two factors: (1) There seems to be little specific knowledge of the structures that are present in the normal broad ligament. (2) Of even greater importance were the contradictory and frequently inadequate or even erroneous concepts of the embryonic development of broad ligament structures. One of the erroneous concepts was traced to the assumption that details in the embryonic development of the rete in the tortoise were directly applicable to man.

The terminologic welter, histologic mélange, and embryologic diversities left us in a state of mind that could best be described as one of "chaotic confusion." It was, therefore, decided to study the embryonic development of broad ligament structures, the normal adult broad ligament, both in routine and in serial section, and, finally, the abnormal broad ligament. That portion of the study having to do with the histogenesis of broad ligament cysts will be presented here. A simple classification based on histogenesis will be proposed.

*Presented, by invitation, before the New York Obstetrical Society, Nov. 11, 1947.

†Supported in part by a grant from Ciba Pharmaceutical Corporation.

The data will not include a statistical study, nor consideration of tumors of mesodermal origin. It will be concerned with epithelial elements normally found in the broad ligament and retention cysts arising therefrom.

Materials

Fourteen serially sectioned specimens from embryos and newborn were studied. These were obtained from 14, 22, 24, 27, 80, 80, 95, and 95 mm. embryos; 5, 7, and 8 month fetuses; and three newborn infants.

Adult material was obtained from routine blocks of 598 normal and pathologic broad ligaments, tubes, and ovaries. This figure refers to the number of operative patients. In some instances, both broad ligaments were available for study. In addition, the lateral half of eleven broad ligaments was serially sectioned at 10 microns. These preparations include the base of the ovary and the mesosalpingeal portion of the tube. The remainder of the block from four routine preparations was also serially sectioned.

Some of the details and differential points to be considered later are based on finer histologic features. They necessitate microscopic preparations of high quality. The routine pathology slides of some institutions, at least, would not meet this specification. Autolysis and desiccation result from excessive delay in placing the operative specimen in the fixative. Harsh fixatives, such as the commonly used 10 per cent formalin, cause undue shrinkage and distort cell structure. Rushing tissues through an Autotechnicon and careless work by technicians cause further damage.

The older routine sections used in this study were not prepared in an ideal manner, since they were fixed in 10 per cent formalin. All the more recent tissues, however, (approximately 150 operative specimens) were immediately placed in Bouin's fluid in the operating room. Microscopic preparations were made by Miss Mildred Milligan, to whose technical competency and artistic skill part of the credit for this study must be attributed. Credit must also be given to the equally competent Mrs. Karen Gustafson, who prepared the majority of the serial sections.

The stains used were: routine hematoxylin and eosin, the Milligan Stain (Milligan 1946), iron hematoxylin-mucicarmine, and glycogen stains. Hematoxylin and eosin is satisfactory for routine purposes but is unsatisfactory for some histologic details.

Embryology and Definition of Terms

Mesonephric Structures.—In the embryo, the mesonephric duct and some 80 mesonephric tubules are part of a urinary excretory apparatus, the mesonephros. With formation of the definitive or metanephric kidney, the mesonephros almost completely disappears. However, the caudal one-third or one-fourth of the mesonephric duct and the 10 to 15 mesonephric tubules connected with the cranial part of the duct remnant are preserved. In the male, these remaining tubules and duct become the spermatheca system. In the female, the mesonephric tubules and that part of the duct in connection with them are consistently preserved and persist as such throughout adult life. The tubules are grouped together and extend from the most lateral portion of the hilum of the ovary toward the tube. Near the tube, they communicate with the mesonephric duct which runs parallel to the course of the tube.

The mesonephric tubules and duct found in the adult broad ligament actually represent a continued existence of the same structures found in the

embryo. We shall, therefore, refer to them as mesonephric tubules and mesonephric duct. We see no reason to call them by any other of the confusing names with which they have been saddled (Table I). We object in particular to the use of a man's name (no matter how illustrious) in designating anatomic or histologic structures or pathologic conditions. The name of a structure should, if possible, have functional, histogenic, or at least morphologic, significance. It would appear better to avoid confusion than to add to it by the use of personalized nomenclature.

Paramesonephric Duct.—Our bias against using the names of individuals for structures also extends to “Müllerian duct.” We prefer a term used by

TABLE I

PROPOSED TERMINOLOGY	COMMONLY USED TERMINOLOGY
Mesonephric body	Wolffian body, organ of Rosenmüller, epoophoron, parovarium, Kobelt's tubules, parovarial tubules
Mesonephric duct	Wolffian duct, longitudinal tubule of epoophoron
Mesonephric tubules	Wolffian tubules, Kobelt's tubules, epoophoral tubules, transverse tubules of epoophoron
Paramesonephric duct	Müllerian duct
Oviduct Uterine tube	Fallopian tube
Accessory oviducts	Accessory Fallopian tubes

many modern embryologists, “paramesonephric duct.” For “Fallopian tube,” we shall use the anatomically preferable name, “uterine tube,” or the functional term, “oviduct.” The latter is a better descriptive name.

The paramesonephric duct is a latecomer compared to the mesonephric duct. The latter gets its start at about 4.5 mm., while the former does not develop until about 10.0 mm. (4 weeks and almost 6 weeks, respectively). This is fortunate, since the paramesonephric duct seems unable to differentiate as it should, without the mesonephric duct to guide it. It has long been known that absence of a kidney, in certain patients, is due to lack of development of mesonephric duct (normally the ureter must bud off from the mesonephric duct and reach the metanephric anlage for formation of the kidney). In these same patients, only the most lateral part of the tube is present, and the same side of the uterus is missing, so that it is unicornuate. Gruenwald (1941) has very beautifully demonstrated the cause for this. He interrupted the continuity of the mesonephric duct early in the development of the chick embryo. The later-developing paramesonephric duct never reached its normal destination (urogenital sinus). Its course was terminated at the area where the mesonephric duct had been severed. He has also demonstrated in the human being that the growing, advancing tip of the paramesonephric duct travels under the basement membrane of, and is guided in its course by, the already existent mesonephric duct. As previously noted, the paramesonephric duct begins its development at about 10 mm. On the lateral surface and near the cranial end of the mesonephric body, a groove appears in a localized area of thickened epithelium.

This groove invaginates caudalward and into the stroma. The rapidly growing tip reaches and penetrates under the basement membrane of the mesonephric duct and continues its caudalward growth thereunder. This phenomenon is clearly evident in our own specimens (14, 22, 24, and 27 mm.). However, only the continuously growing tip is found under the basement membrane, the older and more cephalad part of the duct being just external to the basement membrane, and then, finally, separated from the mesonephric duct by intervening stromal cells.

The paramesonephric duct reaches its objective (the urogenital sinus) in this manner at about 30 mm. (approximately 9 weeks). When finally differentiated, the cranial one-third of the paramesonephric duct becomes the oviduct or uterine tube.

While the paramesonephric duct is coursing downward to reach the urogenital sinus, the fimbriae are being formed. This process is most clearly described by Felix in Kiebal and Malls' "Human Embryology" (1912). The original epithelial invagination forms the primary or definitive ostium of the tube. In the area surrounding this ostium, multiple secondary invaginations occur, grow downwards, develop a lumen, reach, and, finally, penetrate through to the lumen of the paramesonephric duct. These secondary invaginations en masse form the anlage of the fimbriae, which develop by a process of epithelial and then luminal coalescence.

The probable fate of secondary invaginations that do not contact the original paramesonephric duct, but continue their irresponsible way, unguided by the mesonephric duct, will be discussed in later sections.

I. Structures of the Normal Broad Ligament

Mesonephric Structures.—In the majority of gynecologic textbooks, the normal structures of the broad ligament are treated in a rather cavalier manner and dismissed from further consideration after a few cursory sentences or paragraphs. Frequently, however, a copy or "modification" of a drawing made in 1905 is included. This drawing had much artistic merit but, unfortunately, it portrays the mesonephric tubules as being fairly evenly spaced throughout the broad ligament. Actually, mesonephric tubules are not uniformly spaced throughout the broad ligament. Instead, the mesonephric tubules (with the exception of those inconstantly present, mesial to the vessels in the mesovarium [paroophoron]—with which we are not concerned) are found in a specific portion of the broad ligament. Normally, the ovarian blood vessels course through and occupy, in so doing, the middle third of the mesovarial area. The mesonephric tubules are closely grouped in the most lateral one-third of the mesovarium and extend up through the most lateral mesosalpingeal portions of the broad ligament. Various authors have previously reported this fact. (Kohelt, 1847, Duthie, 1924, Watkins, 1933.) It can easily be confirmed by inspecting the freshly removed ovary and broad ligament held up against a fairly strong light.

The mesonephric duct (Figs. 1 and 2) is found in microscopic sections fairly close to, but external to, the musculature of the oviduct. It is usually moderately convoluted, and several cross sections may therefore be seen in one slide. It has its own discrete muscular investment, with an unusual arrangement of inner longitudinal and outer circular fibers. The muscular layer is



Fig. 1.—Several cross sections through a convoluted mesonephric duct. The muscle coats are well developed and the epithelium is simple cuboidal. $\times 600$.

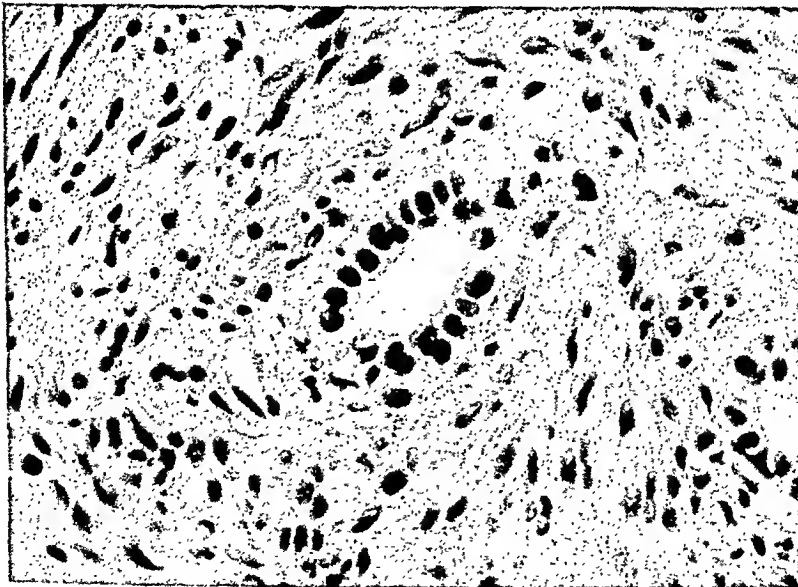


Fig. 2.—Mesonephric duct. Higher magnification of duct from Fig. 1. $\times 1995$.

usually heavier than that of the mesonephric tubules. The duct epithelium in almost all of our specimens has been low cuboidal with mesially placed, moderately vesicular nuclei. In the few exceptions, the epithelium has been somewhat higher, with a tendency of the cytoplasm to "stream out" into the lumen. No cilia have been found in the duct epithelium.

The mesonephric tubules (Fig. 3) are usually more highly convoluted than the gently undulating mesonephric duct. Its musculature, according to Duthie (1924), also consists of an inner longitudinal and an outer circular layer. This has been true in most of our specimens, but not definitely demonstrable in others. Deep in the broad ligament (in the mesovarial area) as the mesonephric tubules near the rete, the muscular coat is lost.

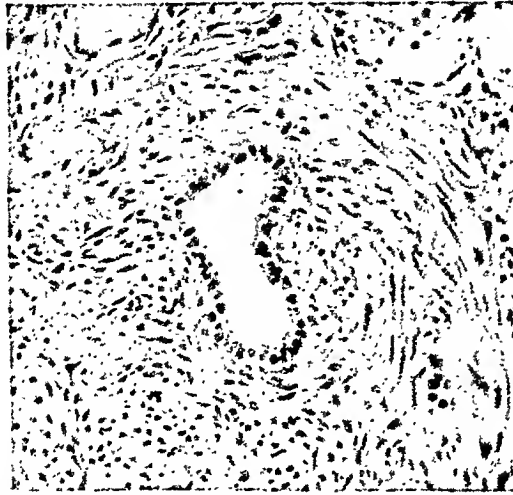


Fig. 3.—Mesonephric tubule. Note well-developed muscle sheath. Epithelium is more complex than in the mesonephric duct. See Fig. 7 for greater magnification. $\times 840$.

The epithelium of the tubules is more specialized and more prominent than that of the duct. The cells, while low columnar or cuboidal, are quite large. Two types are present, ciliated and nonciliated. The cytoplasm of the ciliated cells stains very lightly; so much so that, occasionally, the cell looks vacuolated. Their nuclei are large, usually round, and centrally located in the cell. With an iron hematoxylin or a Milligan trichrome stain, the basal corpuscles of the cilia make a prominent darkly staining line just proximal to the luminal surface of the cell. The cilia are prominent with the above stains but are easily visible with routine hematoxylin and eosin stain.

The cytoplasm of the nonciliated cell stains more darkly and thus contrasts with that of the ciliated cell. Both types of cells are usually the same height, although the nonciliated cells may be somewhat narrower than the ciliated. The nuclei of the nonciliated cells are usually centrally placed and oval in shape, with granular chromatin. Occasionally these cells appear compressed and elongated.

This description of mesonephric tubule epithelium is applicable to a vast majority of tubules in both our routine and serially sectioned specimens. In a very few specimens, atypical, presumably hyperplastic epithelial changes have been noted. In four specimens, epithelium has been found that is identical to that of the male homologues (efferent tubules in one and conus epididymis in three). These atypical epithelia will not be discussed further in this presentation.

In the literature, descriptions of the epithelium of the mesonephric tubules are (to say the least) somewhat varied. The descriptions vary from simple cuboidal epithelium (Novak, 1947), cuboidal to columnar epithelium (Duthie, 1924), columnar epithelium (Cole, 1910), cuboidal to columnar epithelium with structures which look like cilia but are artifacts (Opocher, 1939, Lucchetti, 1937), cuboidal to columnar epithelium that may bear cilia (Piersol, 1916, Craig), to ciliated columnar epithelium (Doran, 1884). While some of these erroneous descriptions may be due to inadequate observations, it is believed that most are due to delayed fixation, use of harsh fixatives, or inadequate histologic technique.

Few observers have differentiated the epithelium of the mesonephric tubules from that of the duct. Doran, in the latter part of the last century, however, in his book on ovarian and broad ligament tumors, did this very clearly. While he erred in stating that the tubule epithelium consisted entirely of ciliated columnar cells, no one can criticize his description of the "simple cuboidal" epithelium lining the mesonephric duct.

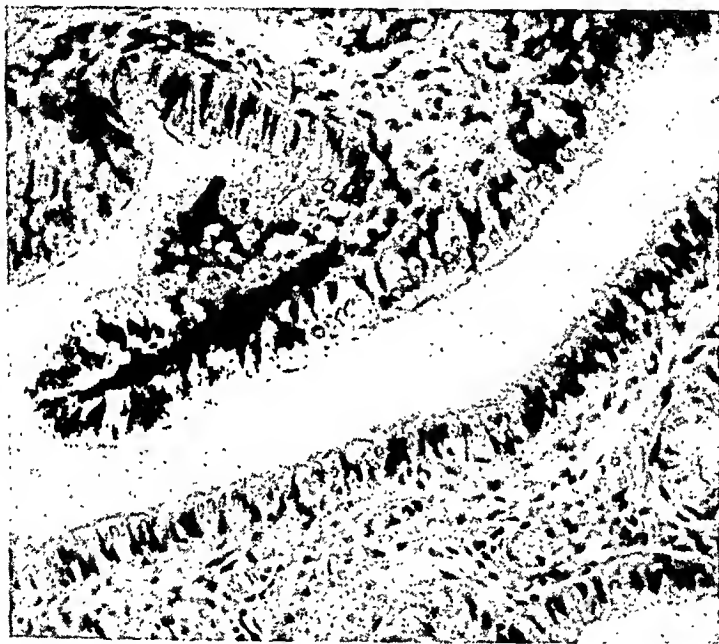


Fig. 4.—Normal oviduct epithelium in estrogenic phase. $\times 840$.

Paramesonephric Derivatives.—The general anatomy of the oviduct will not be considered here. The histology of the epithelium (Fig. 4) is, however, pertinent. It is similar to the epithelium of the mesonephric tubules in that it contains both ciliated and nonciliated cells. The latter, in the oviduct, are commonly called "secretory cells." In addition, another type of cell has been described. This so-called peg cell, however, probably represents only a much squeezed and elongated secretory cell and will not be considered further.

The actual height and relative height of the secretory and ciliated cells vary with different stages of the menstrual cycle. During the estrogenic or preovulatory phase, the epithelium is quite high—all the cells being high columnar and of the same height. The luminal surface during this stage is, therefore, quite smooth and regular. In the progestational phase (secretory), the secretory cells are relatively higher than the ciliated cells. The latter at this stage are large, plump, low columnar cells. The secretory cells are still elongated. However, they have much less cytoplasm, and their nuclei may project into the lumen, covered by a thin layer of cytoplasm. During early menses (and pregnancy)

the epithelium is much lower, the luminal surface even more irregular, with practically bare secretory nuclei projecting well above the surface of the ciliated cells.

As in the mesonephric tubules, the cytoplasm of the ciliated cells stains very lightly and contrasts with the cytoplasm of the secretory cell.

The appearance of the epithelium in the postmenopausal woman has not been studied in any detail. However, in the majority, it is lower but resembles that of the estrogenic phase of the menstrual cycle. Only rarely has cuboidal atrophic-appearing epithelium been encountered.

In a few of the routine sections, we have noted epithelial tubules (Fig. 5) in the broad ligament, obviously not of mesonephric origin, whose epithelium was similar to that of the accompanying oviduct. Findings in four of the serially sectioned broad ligaments established the paramesonephric origin of such tubules.



Fig. 5.—Paramesonephric tubule from the same broad ligament as in Fig. 3. See Fig. 7 for greater magnification and comparison with mesonephric tubule. $\times 840$.

In two of the serials, single tubules were first noted in the substance of the broad ligament at about the junction of mesovarium with ovarian hilum. Both penetrated and ended blindly in the ovarian hilum proper. These tubules extended outward (from the hilum) with few or no convolutions, until both terminated with patent lumina on the surface of the mesovarium adjacent to the "ovarian" fimbria, which happened to be present in both instances. In both specimens, the plane of the section was approximately at right angles to the course of the tubules. One was present for 64 sections or 640 microns. The other was present for 90 sections or 900 microns. Their epithelium had the histologic characteristics of oviduct epithelium and showed the same phase of hormonal response as did the accompanying oviduct.

In a third, a paramesonephric tubule penetrated into the hilar region and terminated blindly near the rete. This tubule differed, however, in that, peripherally, it communicated and was continuous with the lumen of a well-developed accessory oviduct. This particular specimen will be mentioned again when accessory oviducts are considered.

In a fourth specimen, a similar cross-sectioned tubule was noted in the broad ligament at about the junction of mesosalpinx and mesovarium. It was

surrounded on all four sides by mesonephric tubules. Followed in serial section, it abruptly became a complex structure whose long axis was at right angles to the original tubule and extended in the mesosalpinx halfway to the oviduct. This structure was moderately dilated, but insufficiently so to be called a cyst. It was mildly undulating in outline and contained complex "villi" that, except for a moderate amount of "stunting," were identical to those of the oviduct. The epithelium of this structure was similar to that of the accompanying oviduct and was in striking contrast to the adjacent mesonephric tubule epithelium.

This structure can be interpreted only as a blind intraligamentous accessory oviduct and probably had the same origin as the analogous structures to be described later—true accessory oviducts.

In two other serially sectioned specimens, intraligamentous tubules of paramesonephric origin have been encountered. When traced, however, they terminated in intraligamentous cysts.

A final, rather curious, elongated structure should be mentioned. This was in, on, and above the surface of the mesosalpinx of one of the first specimens discussed in this section. Followed in the serial sections, it was found to be above and free from the surface of the broad ligament at each end, with its middle part subserosal. It was lined with oviduct type epithelium throughout and had a well-developed muscular sheath. The smaller free end was moderately dilated. The other appeared bulbous, moderately dilated, and contained many short but typical tubal "villi."

Accessory Oviducts.—Accessory oviducts are usually small structures of variable length and width projecting out from the broad ligament and with open fimbria.

The authors are in somewhat of a quandary as to how to classify accessory oviducts—as a normal or an abnormal finding. Certainly they are too common to be considered pathologic. Their exact incidence is not known. They are inconspicuous structures and are usually not noted by the surgeon, except in the few reported cases where they have been the seat of an ectopic pregnancy. Unfortunately, no record was kept by us as to their relative frequency in the operative specimens.

In the unselected routine pathologic slides examined by us, accessory oviducts were clearly present and with patent fimbria in specimens from eleven patients. In one of these, three separate accessory oviducts were present (Fig. 6) and another had two accessory oviducts. Accessory oviducts are truly miniatures of their normal sisters, with the usual "villi" and similar epithelium, showing the same hormonal response as in the true oviduct.

Accessory oviducts have been present in two of the serially sectioned specimens. In one of these specimens, the pedicle of one accessory oviduct was attached to the broad ligament in the mesovarial region. The pedicle of a second, in this same specimen, was attached to the serosal surface of the oviduct a few millimeters away from the attachment of the mesosalpinx. Surprisingly enough, this accessory oviduct had an accessory of its own, which was attached (to the base of its fimbriae) by a relatively long pedicle. Each of these three accessory oviducts had well-developed fimbriae (although smaller than those of the uterine tube) and patent lumina which penetrated down the stalk for a short distance.

In the second specimen, one accessory oviduct was present. It was attached by a broad pedicle or stalk to the broad ligament directly over the hilar region, with one portion of its circumference near the lateral border of the cortex of the ovary. It had well-developed fimbriae. The lumen of this structure was quite wide until about the area of junction with the hilum. Here it abruptly

narrowed, and the resulting tubule penetrated with an undulating course into the hilum, just short of the rete body, where it abruptly terminated. The penetration of the tubule into the hilum in this specimen has been previously mentioned.



Fig. 6.—Hemi-cross section of oviduct and three accessory oviducts. $\times 5$.

There seems to be but one fairly simple explanation for accessory oviducts, paramesonephric tubules in the broad ligament, and, as will be discussed later, for certain cysts. As previously described under "embryology," the fimbria are formed by a process which starts out in a manner similar to that which results in the formation of the main paramesonephric duct. Multiple miniature paramesonephric invaginations develop in the region surrounding the original duct orifice, grow down, and join the lumen of the latter. If one of these invaginating tubules fails to reach the main duct, it seems likely that it continues partial development as a paramesonephric duct in miniature, and this gives rise to the structures that have been described. The apparent helter-skelter or purposeless distribution of these structures in, on, or under the surface of contiguous structures can also be explained. The main paramesonephric duct grows caudalward and reaches its proper objective by following along the surface (and under the basement membrane) of the already existent mesonephric duct. If the latter fails to develop completely, the development of the duct is correspondingly limited. The paramesonephric duct, therefore, does not have an inherent ability, in itself, to develop in a normal manner. It seems logical to believe that these miniature paramesonephric ducts have this same lack of ability as to direction and extent of growth.

In 1907, Robert Meyer rather severely criticized J. Koch for having reported a tubule derived from the base of the ovarian fimbria and penetrating into the hilum of the ovary as a "Müllerian" duct derivative. Koch's tubule apparently was identical with those of the first two specimens described in this section and was similar to that of the third, except that the latter terminated in the lumen of an accessory oviduct.

To Meyer, it was obvious that these tubules were of mesonephric or even pronephric origin, and certainly not a derivative of the cranial part of the main paramesonephric duct. We agree that they do not originate from the main or primary paramesonephric duct. If the epithelium of the tubule discussed by Koch is similar to that of ours (no histologic details were presented), we are unable to agree with the first part of Meyer's conclusions. The epithelium of these particular tubules was obviously of paramesonephric origin. The junction of the tubule in this region, in the third specimen, with the lumen of a well-developed accessory oviduct is certain evidence that paramesonephric tubules can occur in this region. It seems likely that Koch's specimen and our specimens represent the end results of the unguided wandering of a secondary invagination that was a little too dilatory in its attempt to commune with the primary paramesonephric duct.

Differences Between Mesonephric and Paramesonephric Structures.—As previously noted, the epithelium of mesonephric tubules and that of the oviduct bear some resemblance in that both are made up of ciliated and nonciliated cells. In both, the general distribution and arrangement of the two types of cells are about the same. In both, the ciliated cells stand out in stained sections, due to the almost complete lack of cytoplasmic staining. It is possible, however, to distinguish the two epithelia with a reasonable degree of certainty.

The most obvious difference is that of *nuclear and cell size*, particularly evident in the ciliated cell. In a sense, the mesonephric epithelium gives an impression of being a junior edition of the oviduct epithelium. To confirm our impression, the cell height and nuclear diameter of ciliated cells in 18 specimens have been measured with a micrometer ocular. In eight specimens, measurements were made on ten nuclei and cells in mesonephric tubules and the same in the oviduct, the cells being chosen at random. In ten other specimens, the procedure was similar but only five measurements were made. The average results were practically identical, whether five or ten measurements were made. It is, therefore, presented in the table as the average from the total of 18 patients (Table II). The difference between the nuclei of the two types of epithelium

TABLE II. COMPARISON OF MESONEPHRIC AND PARAMESONEPHRIC CELL AND NUCLEUS SIZE

	OIDUCT CELL	MESO- NEPHRIC CELL	DIFFER- ENCE	OIDUCT NUCLEUS	MESO- NEPHRIC NUCLEUS	DIFFER- ENCE
Number of cases	18	18		18	18	
Average \pm St. error in microns	18.56 \pm 0.96	12.88 \pm 0.47	5.74 \pm 1.12	9.46 \pm 0.28	7.47 \pm 0.14	1.99 \pm 0.33
Ratio			5.14			6.04
Probability			<0.01			<0.01
Significance			High			High
Area from diameter*				69.99 square microns	43.88 square microns	

*See text.
Method: paired comparison, Snedecor, "Statistical Methods," Iowa State College Press, Ames, Iowa, 1946.

is not so striking when presented in terms of diameter (though it is statistically significant). One does not, however, visually or mentally compare nuclear size in terms of diameter but rather in terms of total area. The area of these essentially round structures was therefore calculated from the diameter measurements. The difference is then more apparent. The paramesonephric nuclei are more than half again as large an "area" as the nuclei in the mesonephric tubule epithelium.

The difference in cell height is obvious, as can be seen in the table and in Fig. 7, the paramesonephric ciliated cell being, on the average, approximately 50 per cent greater than the ciliated cell of the mesonephric tubule.

The mesonephric tubule epithelium has a well-defined *basement membrane*, as does its pathologic derivatives. (This is also true of the duet and its derivatives.) The oviduct epithelium has no basement membrane.

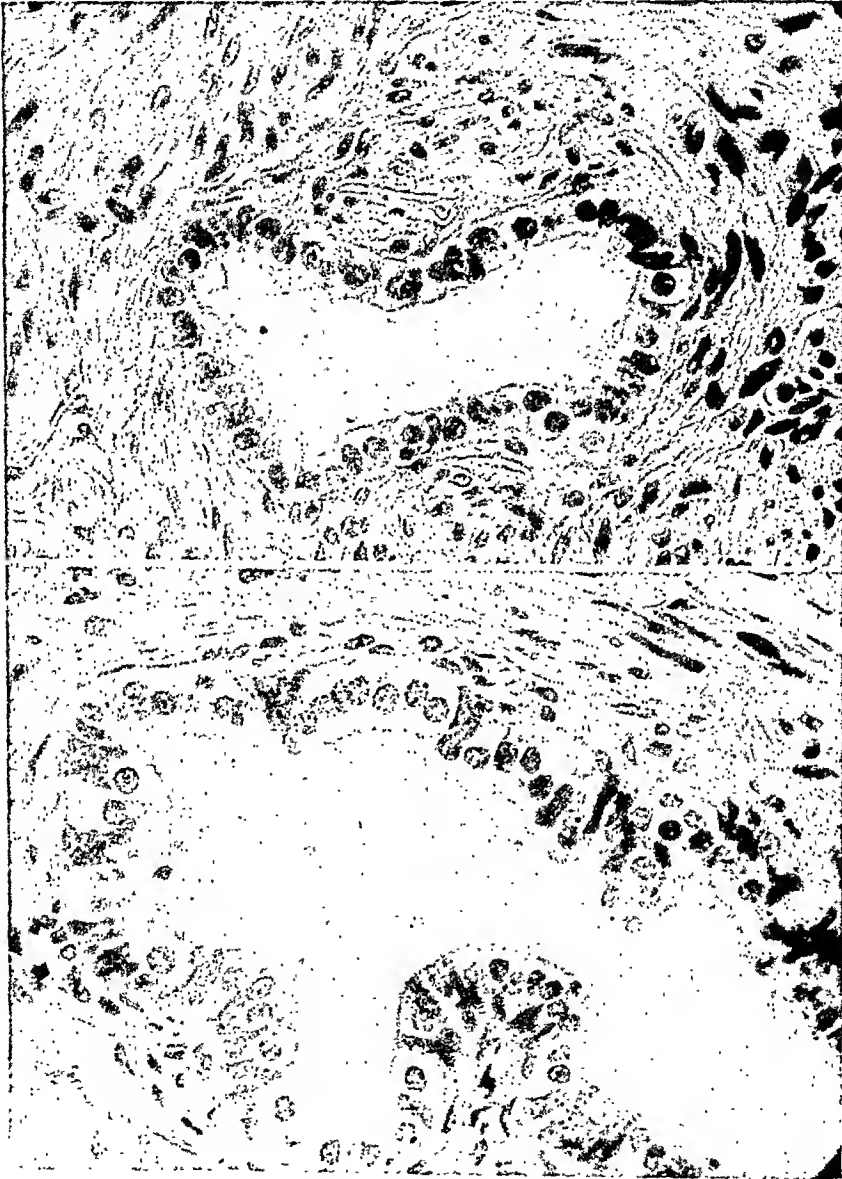


Fig. 7.—Mesonephric and paramesonephric tubules from the same broad ligament and at the same magnification. Note greater size of cells and nuclei in the paramesonephric tubule. $\times 1935$.

Observations on the basement membrane are usually presented in a matter of fact manner—the implication being that this structure is easily recognized and noneconfusable with other structures. This has not been the authors' experience. In sections tangential to the basal epithelial surface, the basement membrane is frequently not visible. In the field being studied, the section must be at right angles to the epithelium before one is justified in stating that a basement membrane is not present. In the ordinary routine hematoxylin and

eosin staining, the basement membrane is a poorly defined structure. In fact, so poorly defined that a continuous smooth-surfaced row of basal epithelial cells with well-defined cell borders may be confused with it. This may be the case at the base of the ciliated cells of paramesonephric epithelium. However, at the base of the secretory cells, the absence of the basement membrane is obvious.

The so-called *villi* are structures characteristic of the oviduct. Few are in reality villi but are transverse sections through folds or plica. Villi are not present in mesonephric tubules and can hardly be confused with the occasional irregularities produced by sections through a sharply angulated bend in the tubule, or with the more minor irregular projections of the epithelium into the tubule lumen, due to rapid and extensive shrinkage of tissue with the use of harsh fixatives.

While *cyclic changes* in the mesonephric tubules during the menstrual cycle have not been studied in detail, it is known that the mesonephric tubule epithelium does not show the characteristic oviduct epithelial changes of the progestational part of the cycle, menses and pregnancy. The projecting nuclei and irregular luminal surface of oviduct epithelium are not characteristic of mesonephric epithelium.

II. Cystic Structures

The authors were in somewhat of a quandary as to exactly how large the dilatation of an epithelial structure had to be before a cyst could be considered present. It was arbitrarily decided that only those would be considered that were macroscopically visible. One hundred and one such cysts were found, including both intraligamentous and pedunculated. An endeavor has been made to determine whether each cyst was of mesonephric or paramesonephric derivation. This determination has been made in 87 of the cysts. In seven specimens, we were unable to determine the origin of the cysts. In seven other specimens, the microscopic preparations were of too poor quality to allow any such determination.

Pedunculated Cysts.—Most authors believe that two types of pedunculated cysts exist. They are differentiated by the site of origin of their pedicle. If it arises on or near the fimbriae, it is called a "hydatid of Morgagni." As a small structure, this is so common as practically to be considered normal. The other is stated to have a pedicle which arises more mesially (closer to the uterus) and from the surface of the broad ligament. The derivation of these hydatids may or may not be the same, depending on what authority is being quoted.

Modern embryologists (Arey, 1942; Hamilton, Boyd and Mossman, 1945; Patten, 1946; Krafka, 1942) and others (Doran, 1884, Schiller, 1946) quite uniformly agree that the hydatid of Morgagni is a paramesonephric derivative. An equal number of authorities, however, believe it to be of mesonephric origin (Pierson, 1916; Quinet, 1944; Watkins, 1933; Craig, Nordlander, 1941; Kieth, 1923). A rather unique view that it has pronephric origin is held by Peel (1944) and by Gilbert and Sheoray (1941). Present-day embryologists are unanimous that, with the exception of the pronephric duct, which doubles in brass and becomes the mesonephric duct, all pronephric structures disappear.

The "hydatid of Morgagni" results from a developmental error in the formation of the fimbriae. One of the secondary invaginations never reaches the main duct. It continues development as one of the previously described accessory oviducts, with the exception that it loses its luminal connection with the primitive peritoneal cavity. Having no orifice, it undergoes cystic dilatation. It, therefore, actually is a hydropic accessory oviduct.

In our own preparations, the early stages in the previously described development of the fimbriae are well demonstrated. In a 22 mm. embryo, epithelial invaginations near the ostium of the main paramesonephric duct are clearly evident, with their down-dipping epithelium reaching but not penetrating the main duct epithelium. In a 24 mm. embryo, these invaginations are more obvious and some of them communicate with the main duct. This is also the case in a 27 mm. embryo. In the broad ligament of an 80 mm. embryo, a pedunculated accessory paramesonephric duct remnant is attached to the mesosalpinx in the immediate vicinity of the developing fimbriae. A similar structure was found in a 95 mm. embryo. The epithelium in these structures is identical with that of the main paramesonephric duct. They have, however, no orifices. If the embryos had lived, it seems likely that these structures were destined to become hydatids of Morgagni. Interestingly enough, an identical structure was attached to the mesosalpinx of the other side of the 80 mm. embryo. It differed, however, in that the point of attachment of its stalk was overlying the mesonephric tubules (those destined to persist) and was some distance from the paramesonephric duct fimbriae. Its epithelium was identical with that of the paramesonephric duct and did not resemble that of mesonephric origin.

A structure similar to that first described in the 80 mm. embryo has been found in the serially sectioned broad ligament of a near-term fetus. The pedicle was attached in almost immediate contiguity with the base of one of the most lateral fimbria of the oviduct. It had undergone a moderate amount of cystic dilatation and its epithelium was well differentiated and identical with that of the oviduct (similar to adult type epithelium).

Twenty-five pedunculated cystic structures were found in the adult material (both routine and serial sections). This group includes both the "hydatids of Morgagni" (pedicle attached at or near the tubal fimbria) and the so-called "Kobelt cysts" (pedicle not attached in the immediate vicinity of the fimbria).

One tissue was omitted from consideration because of its very poor quality. Twenty-two of the remainder were lined with epithelium identical to that of the tube. In almost all instances, sections of the tube were also available. In such cases, the cyst epithelium showed the same characteristics of the various phases of the menstrual cycle as did the tube. In 17 of the 22, "villi" were present. These "villi" had the same basic structure as those of the tube. Other characteristics of paramesonephric epithelium were present.

One of the two remaining pedunculated cystic structures had the usual thin wall composed of fibrous and smooth muscle tissue. It was lined, however, by low cuboidal epithelium with a distinct basement membrane. No cilia were present. This epithelium was identical with that usually found in the mesonephric duct. It seems probable that this was a pedunculated mesonephric duct cyst. This cyst was in the immediate region of the fimbria. It seems likely therefore, that it represents a development of the most cranial portion of the mesonephric duct remnant.

There remains one pedunculated cyst. We are uncertain of the origin of this structure, since, in some respects, it resembled paramesonephric derivatives and, in others, mesonephric tubule derivatives.

Even granting that this last specimen was a mesonephric tubule derivative, the final tally on the origin of these pedunculated remains is: paramesonephric 22, mesonephric duct 1, mesonephric tubule 1. This corresponds well with the pedunculated structures seen in the embryos and newborn.

Nonpedunculated Cysts.—The opinions of the various authors as to the derivation of pedunculated cysts were given in the last section. The derivation of those that do not have a true pedicle will be considered here. This group will necessarily include a few small cysts that are sessile.

There is little disagreement as to the nature of the wall of these cysts. They are relatively thin (in contrast with the rare true intraligamentous cystoma, in which the wall of the cyst takes an active part in the growth) and are composed of connective tissue and muscle fibers.

There has been the usual variability in descriptions of the epithelium of these cysts. It has been described as simple cuboidal to flat (Schiller, 1946; Graves, 1929; Novak, 1947), cuboidal to cylindrical (Shaw, 1932; Meigs, 1934), varying in different area from flat to high columnar (Lynch, 1922; Nordlander, 1941; Opoeher, 1939), columnar (J. H. Müller, 1942; Forgue and Crousse, 1925). The cells have been described as ciliated (Graves, Shaw, J. H. Müller) or it has been stated that ciliated cells may be found (Doran, Forgue and Crousse, Craig, Nordlander and Lynch). That "papillae" may be found, or that there is a "papillomatous tendency" has been noted (Lynch, Novak, Nordlander, Opoeher, Craig, J. H. Müller, Doran, Graves, and Shaw). None of these authors noted the resemblance of these "papillae" to tubal "villi." Such is specifically mentioned, however, by Kossman (1912), and also by Meyer (1912) in describing a "parovarial" cyst, 8 cm. in diameter.

Many ideas have been expressed on the derivation of these cysts. The vast majority of authors, however, believe them to be mesonephric in origin (Cole, 1910; Craig; Crossen, 1946; Coblenz, 1882; Doran; Forgue and Crousse; Nordlander; Quinet; Meigs; and Watkins). Doran clearly differentiates two types, those from the mesonephric duct and those from mesonephric tubules. Gilbert and Sheorrry, in 1941, stated that the cysts of any significance are derived from "junctional tubules." These cysts they called "fimbrial cysts"—not because the fimbriae had anything to do with their genesis, but because the fimbriae (and tube) are stretched out over their surface. The junctional tubules, they believe, are derived from pronephric remnants, and, in the embryo, are the progenitors of the rete. Gilbert and Sheorrry obtained their embryological data from Keith's Textbook of Embryology (1923). Keith's data on this subject were obtained from an embryologic article devoted to the tortoise, written by Allen, and published in 1905. The fact was ignored that Allen specifically stated that the *rete in mammals was not derived in this manner from pronephric remnants*.

In a textbook published in 1944, Peel essentially repeated the derivations presented by Gilbert and Sheorrry, including the derivation of "fimbrial cysts" from "junctional tubules."

Young, in a textbook (1944), and Shaw, in an article (1932), believe that some broad ligament cysts are of mesonephric origin, but both also classify "fimbrial cyst" in a separate group, and both derive them from "ovarian remnants." Shaw goes further and states that these latter do not represent retention cysts (as do those of mesonephric origin) "but true neoplasms, for the epithelium is either cuboidal or columnar, and the incidence of papillomas in the wall absolutely excludes an origin from Wolffian remains." The latter part of this statement is no doubt true.

The most unique idea is that presented by Sutton, in 1886, that "probably many, but not all, broad ligament cysts arise from dilatation of lymphatic channels."

Paramesonephric Origin.—In many articles, the possibility of the paramesonephric derivation of broad ligament cyst is considered briefly and then dismissed as unlikely or impossible. This was done, for example, by Cole, in 1912. In 1914, however, he presented a case report of a broad ligament cyst which was near and under the fimbria (also stretching tube and fimbria over its surface). This particular cyst was a diverticulum of the oviduct, as demonstrated by serial section.

In an article summarizing various ovarian, hilum, and broad ligament abnormalities he had seen, Robert Meyer (1912) noted one 8 cm. broad ligament cyst which he derived from an accessory oviduct. In general, though, he believed broad ligament cysts to be of mesonephric origin. Gilbert and Sheorrry also believed that the rare small cysts having epithelium identical with the tube, uterus, or cervix are of paramesonephric origin—accessory oviducts or diverticula therefrom.

Apparently Kossman has stood alone in believing that all broad ligament cysts are of paramesonephric origin. One of his reasons for so claiming, however, was based on a misconception. He believed there was no musculature around mesonephric structures and, since muscle fibers were present in the walls of these cysts, they must be of paramesonephric origin.

In summary, most have believed that broad ligament cysts were of mesonephric origin. A few believe that some may be derived from pronephric remnants. The embryologic data on which these latter claims are based are not very pertinent. The very few remaining investigators were of the opinion that some or all broad ligament cysts may be of paramesonephric origin.

Seventy-six intraligamentous cystic structures, varying in size from 2 mm. to approximately 10 cm., have been found in the present study (in addition to a cystic mesonephric tubule found in the newborn). Six of these have been omitted from consideration because of the poor quality of the tissue. We were unable to be certain whether five other cysts were of mesonephric or paramesonephric origin.

Mesonephric Duct Cyst.—In four of the routine sections, small cysts had the usual relatively thin wall composed of muscle and connective tissue fibers, but their epithelium had a distinct basement membrane and was composed of low cuboidal cells with no cilia. The inner walls were smooth. No villi or papillae were present. The epithelial lining was identical with that usually found in the mesonephric duct. Luckily, a fifth similar cystic structure, whose origin was obvious, was found in a broad ligament that had been serially sectioned. In a single section in the mesosalpinx near the oviduct, there appeared to be multiple small cysts, lined by simple low cuboidal epithelium. Their walls were composed of muscle tissue. The thickness of their walls seemed to vary inversely with the diameter of their lumen. Examination of the serial sections, however, proved that all of the structures were part of a cystically dilated and convoluted mesonephric duct that terminated blindly at the most bulbous end and communicated with mesonephric tubules near the other end (which also ended blindly). These latter tubules were only moderately dilated.

Mesonephric Tubule Cyst.—Thirty-three of the remaining cysts were of mesonephric tubule origin. Their walls had the usual characteristics (Fig. 8). Muscular elements were discernible but were scanty in the larger cysts. This latter fact is also true, incidentally, of the larger cysts of paramesonephric origin. The epithelial cells were plump cuboidal to low columnar, with the previously described arrangement of ciliated and nonciliated cells. Their epithelium was similar in all respects to that of the mesonephric tubules.

We had expected the epithelium to be flattened in the larger specimens, due to intra-cystic pressure, and it is true that, in some specimens, areas could be found with the epithelium flattened and almost squamous-like. However, in every specimen (including those both of mesonephric tubule and paramesonephric origin), most of the epithelium was healthy and showed no appreciable evidence of flattening. The only exceptions to this occurred in cysts in which all of the tissues in the slide were shriveled or shrunken. Such tissues, as previously mentioned, are not included in this study.

In this regard, it must be re-emphasized that the details presented in this study will be found only in tissues that have been treated with respect and care. Few of them will be discernible in the routine preparations of the pathology departments of some hospitals, at least. Delays of several hours before fixation, use of harsh fixatives, rushing tissues through an autotechnicon, and careless technical work combine to produce tissues that are very poor shadows of their former selves. Such factors, no doubt, contribute to some of the misinformation on the subject under discussion.

The histologic details that served as diagnostic points, to differentiate these cysts from those of paramesonephric origin, will be presented in the next section. The diagnostic value of location, as well as the presence of mesonephric tubules in the wall of, or adjacent to, the cyst, will also be considered there.



Fig. 8.—Wall of intraligamentous cyst of mesonephric tubule origin. Note resemblance of epithelium to that of mesonephric tubule in Figs. 3 and 7. $\times 1995$.

Mesonephric tubule cysts of varying size were found in six of the serially sectioned broad ligaments. The smallest ones were completely included in the sections; only part of the wall was included in the others.

One of these small cysts occurred as a spherical cystic structure, fairly close to the uterine tube. It was near, but not in continuity or even contiguity with, mesonephric tubules with whose epithelium it was identical. This cyst occurred, we believe, as a result of the cystic dilatation of an isolated remnant of a mesonephric tubule. Such isolated tubules, in this and in other locations, have been found in our serial sections.

Another was first noted as a single cystic structure in the immediate vicinity of, and partially surrounded by, rete cords and rete tubules. There was no luminal continuity, however, between this structure and the rete. When traced through successive slides, it was seen to be a cystically dilated and highly convoluted mesonephric tubule that progressed toward, but did not reach, the mesonephric duct.

Cysts of Paramesonephric Origin.—The remaining 27 intraligamentous cysts were considered to be of paramesonephric origin. This figure does not include the five intraligamentous cysts of whose origin (mesonephric tubule or paramesonephric) we could not be certain.

The wall of these paramesonephric cysts did not differ from those of mesonephric tubule origin, as described in the previous section. Also similar to mesonephric tubule cysts, occasionally areas of low flattened epithelium were found.

“Villi” were found in 22 out of the 27 specimens. They varied in size, or rather, in apparent length in the various specimens, from relatively minute (but

definite) isolated structures to elongated, fairly complex structures with sub-branches. In general, the number of villi, the ease with which they were found, and their degree of development seemed to vary inversely with the size of the cyst.

The epithelium of these cysts was identical with the previously described oviduct epithelium (Figs. 9, 10). Sections of the uterine tube were available with most of these specimens. The cyst epithelium showed the same response to cyclic changes in the sex hormones as did the tubal epithelium.



Fig. 9.—Wall of intraligamentous cyst of paramesonephric origin from the same broad ligament as Fig. 4. Note similarity of epithelium. $\times 840$.



Fig. 10.—Wall of intraligamentous paramesonephric cyst showing progestational response. $\times 1425$.

Paramesonephric cysts were present in four of the serially sectioned broad ligaments. One of these was first noted as an isolated spherical structure, fairly close to, and between, the rete and a group of mesonephric tubules. Several small villi were present, and the epithelium was in the progestational phase of the cycle, as was that of the uterine tube (a corpus luteum in the late vascular phase was found in the other ovary). In subsequent sections, it was determined that this solitary structure was the more bulbous end of a dilated and gently

undulating paramesonephric tubule. In another serial, a similar structure was found in the mesosalpinx, adjacent, but external, to the uterine tube musculature.

Differences Between Cysts of Mesonephric and Paramesonephric Origin.—In most instances the difference in *cell and nuclear size*, particularly in the ciliated cells, is fairly obvious. These differences are similar to those which have already been described in the sections on normal oviduct and mesonephric epithelium. In deciding whether a cyst is of mesonephric or paramesonephric origin, comparison of the epithelium of the cyst with that of the oviduct in regard to nuclear and cell size is very helpful, as is comparison with the epithelium of near-by mesonephric tubules.

The epithelium of cysts of paramesonephric origin shows the same response to sex hormones as does the tubal epithelium. This in itself is of utmost value in differentiating the two types of cysts. If the tubal epithelium shows typical progestational, menstrual, or pregnancy changes, paramesonephric cyst epithelium will show the same change. Mesonephric cyst epithelium shows no such change. Instead, the relatively smooth luminal surface of the epithelium is maintained, and nonciliated cells are approximately the same height as the ciliated cells. In fact, the presence of a tube for comparison is not necessary, if the cyst epithelium shows typical progestational, menstrual, or pregnancy changes, because it is automatically paramesonephric since mesonephric epithelium shows no such change.

In estrogenically stimulated epithelium of paramesonephric origin, ciliated and secretory cells are of approximately the same height. The luminal surface, therefore, no longer has the "uniform irregularity." However, there is, in this phase, definite increase in cell and nuclear size (Cowdry's "Special Cytology"). This exaggerates the difference in this regard between paramesonephric and mesonephric epithelium, and thus actually aids in differentiation between the epithelia of cysts of mesonephric or paramesonephric origin.

The villi in these cysts have almost uniformly been termed papillae or papillomatous processes. Properly used, papillae are projecting nipplelike structures. Actually, these processes are typical of oviduct folds or villi, both as to epithelium and stroma. Their presence is diagnostic of a paramesonephric origin of the structure concerned. No such structures have been observed in normal mesonephric tubules or duct, nor in cysts whose origin can be definitely traced to mesonephric tubules, in the serial sections. The only vague possibility of confusion may occur in routine sections, where apparent intraluminal projections may be formed in acutely angulated, cystically dilated, convoluted mesonephric tubules.

Absence of *basement membrane* in oviduct epithelium (at least in the ampullary and fimbrial portions), paramesonephric tubule epithelium, and paramesonephric tubule cyst epithelium was noted relatively late in this study. The absence of a basement membrane in uterine tube epithelium is ignored in textbooks of histology, and even in the cytological bible, Cowdry's "Special Cytology." The presence of a basement membrane can sometimes be noted with a high dry in hematoxylin and eosin routine preparations. Its presence or absence can be determined only with consistent accuracy, however, under an oil immersion lense, and preferably with iron hematoxylin stains.

In the tissues examined for this detail, and under these conditions, a basement membrane was present in cysts which by all other criteria were of mesonephric tubule origin. It was not present in those of paramesonephric origin examined under similar conditions.

Various authorities have stressed the location of the cyst as of extreme importance in determining the origin of the cyst. For example, the position of a so-called "fimbrial cyst" (Gilbert and Sheorrey, Peel, Shaw), situated in

the lateral portion of the broad ligament with the fimbria and tube stretched over its surface, necessarily indicates its pronephric origin. Actually, any cyst of any origin (excluding the extremely rare cyst originating mesial to the ovarian artery) of "clinical" size necessarily causes the tube and fimbria to be stretched out over the surface.

The available space in the broad ligament being what it is, it seems logical to us that any and all cysts over a few centimeters in diameter would fill this space and thus be indistinguishable on this particular basis. Certainly, in the material available to us, intraligamentary cysts of mesonephric tubule or paramesonephric origin showed no evidence of being distinguishable on this basis. Since the mesonephric duct normally courses closer to the tube than the mesonephric tubules, one would expect the smaller cysts of this origin to be very close to the oviduct. As a matter of actual fact they were, but similarly sized cysts of mesonephric tubule or paramesonephric origin were also found in different specimens in the same area.

Analogously, one might think it quite logical that small cysts located near the rete would of necessity be mesonephric tubule in origin rather than paramesonephric. As a generality, this might usually be true, but as a necessary criterion of the origin of a small cyst at hand, it has no value. As previously stated, paramesonephric cysts were found in the serials (and also in routine specimens) developing relatively close to the rete.

It, therefore, seemed to us that the precise location within the broad ligament of a specific cyst is not necessarily indicative of its origin.

The presence of mesonephric tubules in or near the cyst wall is indicative, according to some authors, of its mesonephric origin. We have no doubt that one is more likely to find mesonephric tubules in or near the wall of a mesonephric cyst than of a paramesonephric cyst. However, mesonephric tubules have been found in or near the wall of some paramesonephric cysts. It, therefore, seems doubtful that their presence could be used as the criterion for diagnosis of a specific cyst.

A simple, logical histogenic classification of broad ligament retention cysts is as follows:

- I. Mesonephric origin
 - A. Mesonephric duct cyst
 - 1. Intraligamentous
 - 2. Pedunculated
 - B. Mesonephric tubule cyst
 - 1. Intraligamentous
 - 2. Pedunculated
- II. Paramesonephric origin
 - A. Paramesonephric cyst
 - 1. Intraligamentous
 - 2. Pedunculated

Conclusions

1. Much of the existing confusion in classifying normal and cystic structures of the broad ligament can be eliminated by discarding terms based on proper names and using those having histogenic significance.

2. Certain well-developed structures derived from the embryonic mesonephros are present in the adult broad ligament, and can easily be demonstrated in properly fixed, properly sectioned, and properly prepared tissues.

3. Mesonephric ducts, mesonephric tubules, and paramesonephric structures, as well as their respective cystic derivatives, have an individual and a characteristic histologic appearance; each can be identified with ease.

4. It is possible to classify most broad ligament cysts on the basis of the character of their lining epithelium; but it is impossible to classify them accurately on the basis of their location in the ligament.

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Discussion

DR. ROBERT T. FRANK.—I was brought up in the old-fashioned way and thought in terms of the Wolffian duct, the Müllerian duct, Gartner's duct, epoophoron and paraophoron, and my reaction to this paper was at first one of revolt at a new nomenclature. However, when I saw the huge material and the tremendous amount of work and research that he and his co-workers had expended on this subject, I was willing to forgive them and went to work to brush up my forgotten embryologic knowledge. I was amply repaid, because he has clarified a very mixed-up and little-understood subject in a surprising fashion. I warn him, from personal experience, that it is very difficult to change a well-established nomenclature. However his method of classification really clarifies the subject. I used to shy away from it and waded through I do not know how many of Robert Meyer's pamphlets telling of these things and got very little knowledge from them, but after having read this paper and studied it carefully, I have gotten considerable satisfaction from it. Perhaps to help you understand some of it, I have a few slides which I want to show and which will give you an idea of how I worked so as to get used to this new nomenclature.

Dr. Gardner has introduced order into this field, but it probably is of greater interest to the pathologic than to the clinical branch of gynecology. From the clinician's point of view, you get cystic structures in the broad ligament. The smaller ones are usually an incidental find; the larger ones are felt by the clinician in his pelvic examination and sometimes induce his exploration of the abdomen for intraligamentous tumors and sometimes non-intraligamentous ones, which are pedunculated. He has the satisfaction of knowing, from what Dr. Gardner and other observers have found, that malignancy is practically unknown in these tumors. I believe that Robert Meyer described two adenocarcinomas, arising in what he felt were the lower ends of the mesonephric duct, which he called Gartner's duct. With that exception, I don't know of any malignancy arising from this source. If large, there is serious difficulty in extirpation because some of them hug the ureter.

I recall a striking case which caused me a great deal of trouble—a woman came to me in the later months of pregnancy with tremendous varicosities of the vulva. She had a bulging cystic mass which practically closed off the vagina and bulged into the buttocks. At that time I could not examine her much further and delivered her by cesarean section (this is many years ago). After full involution, the varicosities had greatly diminished, but she had a string of large cysts which started in the buttocks, went along the vagina, went through into the broad ligament and the uppermost one was almost pedunculated in the broad ligament, causing extreme difficulty of extirpation, which had to be done both from above and below.

I will say that I leave here with the feeling that in the future I will be less confused when I see any of these structures under the microscope.

DR. ANDREW A. MARCHETTI.—I have little to add to Dr. Frank's discussion.

One point which interested me was the fact Dr. Frank brought out, namely, that the structures of the paramesonephric duct, or the Müllerian duct, reacted to the estrogenic and the corpus luteum hormone. This response to hormones is a manifestation of the function to which the derivative of the paramesonephric duct, the oviduct, must adapt itself in the reproductive cycle.

DR. BENJAMIN P. WATSON.—I have always been in favor of discarding proper names for structures and everything else. It is the most confusing thing in medical, surgical, and gynecologic literature. People speak to me about So-and-So's operation and I have to ask, "What operation is that?"

Let us discard these proper names and give them proper embryologic, histologic or pathologic descriptions.

DR. HOWARD C. TAYLOR, JR.—The first question I would like to ask is about this new nomenclature. I agree that this is an important advance from the complicated terminology involving the use of a lot of personal names. I wonder why Dr. Gardner, when he

was producing this revolutionary nomenclature, did not go further and avoid the confusion between "mesonephric" and "paramesonephric." I do not see why the duct which eventually forms the uterus and tube should be named in relationship to its embryonic position, next to the duct of the mesonephros. Why should it not be named the "premesonephric" duct? So, having thought of this subject for the last forty-five minutes since Dr. Gardner brought it up, I raise the question why, when he was making changes in nomenclature, he did not devise a terminology which would be relatively easy for the practical person to follow and remember.

The second question I would like to raise is whether he may be substituting simply one piece of dogma for another. He has attacked the designation of certain structures in the broad ligament as of mesonephric origin, or of paramesonephric origin, on the basis of their general topographic relationship in the broad ligament, to the oviduct or other structures. On the other hand, he is making the assumption that, because certain histologic structures in the broad ligament possess a certain physiologic capacity to respond to certain hormones, they may be regarded as derived from certain embryonic structures which he has named.

Many of the structures in the female pelvis are subject to constant morphologic change. In the pelvic peritoneum you may get cilia and endometrial-like tissues, even mucus-producing cells. These changes are an indication of the transformation, regardless of origin, which may take place in this region. Therefore I would like to be certain that structures in the broad ligament with a low columnar epithelium and with definite basement membranes are derived from embryonic mesonephric structures, and those which have less definitely basal membranes, and those which tend to high columnar epithelium are, as examples, derived from paramesonephric or premesonephric epithelium. I would like to be reassured that Dr. Gardner is not substituting one assumption for another by discarding identification through topography and accepting an equally uncertain identification through histology.

DR. CLAUDE E. HEATON.—I, for one, am loathe to part with all eponymous nomenclature. Kaspar Wolff was one of the founders of modern gynecology. Surely, he deserves to be remembered, and it would seem easier to remember the term Wolffian body than ren primordialis. There are those who would rename the tendon of Achilles. Many of us would agree with the anatomist, F. Wood Jones, that a subject which has lost its tradition is likely to lose its soul. Those interested in nomenclature should consult Jessie Dobson's *Anatomical Eponyms*, published in 1946.

DR. GARDNER (Closing).—To Dr. Taylor I can only say that one of our endeavors has been to introduce to clinicians that terminology which is accepted by authorities in embryology. Furthermore, our studies started with the careful examination of serial sections from embryos; next, we studied broad ligament tissues from newborn infants; and finally, after studying many specimens from adults, we came to the conclusion that the structures which were found in the embryos were the structures that are present in adults.

We are convinced that we are not introducing a new dogma that is without foundation. We believe that these broad ligament structures have not resulted from some type of metaplasia, or neoformation, but are the structures present in the embryo which are carried over into adult life.

THE POSSIBLE SIGNIFICANCE OF ARTERIAL VISUALIZATION IN THE DIAGNOSIS OF PLACENTA PREVIA*

A Preliminary Report

LEO J. HARTNETT, M.D., M.S., ST. LOUIS, MO.

(From the Department of Gynecology and Obstetrics, St. Louis University School of Medicine)

ARTERIOGRAPHY is a method by which the outline of arteries may be seen on x-ray plates following the injection of radiopaque substance. This has been carried out on almost every organ and region of the body, including the arterial circulation of the brain, the chambers of the heart, the extremities and the abdominal organs. Probably the greatest contribution in the field of aortography was made by the urologists, following the reported work of Dos Santos. Aortograms have been reported in this country by Nelson, Doss, Vitt and Melick. The number of cases reported in literature is well over 3,000 and, so far, no fatality has been reported which could be attributed directly to this procedure.

The first report of aortograms on pregnant women appeared in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, in April, 1935. In an article entitled "Abdominal Circulation During Late Pregnancy as Seen by Aortograms" the authors, W. E. Coutts et al., of Santiago, Chili, described this procedure on twelve women in the eighth month of pregnancy. This was performed under spinal anesthesia. The authors reported the death of one patient from meningeal hemorrhage following lumbar puncture. The authors made three valuable contributions. First, in the article is the statement "In Figs. 1 and 3 we can observe the injection of some placental sinuses, and in Fig. 3 certain vascular structures appear, which apparently do not correspond to the maternal circulation, and which we, therefore, believe to belong to the fetal circulation." Second, the authors showed the deviation of the aorta to the left in pregnancy. Third, they observed no ill effects on the mother or fetus immediately following the aortograms. However, there was no report as to the eventual outcome of the pregnancies.

It was conceived that by delaying the time of exposure, following the injection of opaque solution into the aorta, the maternal circulation over the placental site might be visualized by x-ray. This procedure was carried out on 68 women in the later stages of pregnancy.

Preoperative Procedures

The patients selected for this series were obtained from the Clinic of Firmin Desloge Hospital and private practice. Their ages varied from 20 to 35 years. Parity was not considered later, but, in the early stages of the investigation,

*Read at a regular meeting of the St. Louis Gynecological Society, Dec. 11, 1947.

only primiparas were selected. Preoperative routine consisted in a routine workup, including a P.S.P. test and N.P.N. determination. Particular emphasis was placed upon the kidney function of the patients since the opaque solutions, both sodium iodide and Diodrast are excreted by the kidney. All patients were rejected in whom the results of these tests were not within normal limits. The fetal heart tones were checked at intervals and recorded. When it was determined that the patient was a suitable candidate for investigation, she was tested for sensitivity.

Sensitivity Tests

Both sodium iodide, 80 per cent, and Diodrast, 70 per cent, were used in this series. The 40 per cent solution of Diodrast was used for sensitivity tests. An intradermal injection was made, and, if this produced no reaction, 1.5 c.c. were injected intravenously. If no changes, such as headache, swelling of the tongue or nasopharynx were observed after one hour, the patient was considered not sensitive to Diodrast. The patient received 1.5 c.c. of the 80 per cent solution of Na Iodide intravenously, and the temperature, pulse, and blood pressure were recorded at 15 minute intervals for one hour. If no marked changes were observed, it was considered safe to inject the amount necessary for arterial visualization. Transient pain in the arm, shoulder, and chest, on the side of the injection, was a frequent observation and was not considered a contraindication. Symptoms of acute iodism were not encountered in this series; however, two patients were rejected because of a positive intradermal reaction to Diodrast. The patients received an enema three or four hours before the procedure began, and food and fluids were withheld for six hours. Preoperative medication was 1/150 grain of atropine sulfate, given thirty minutes before administration of anesthesia.

Special Apparatus

The pressure apparatus was made by the W. and H. Company for the administration of Pentothal sodium. A 50 c.c. syringe and high pressure tubing at least 20 to 24 inches in length, with a firmly attached glass bulb, with all connections firmly tied onto Luer-Loks, were used to inject the solution through an 18 gauge needle about 15 cm. in length. The arm, as seen in Fig. 1, was attached to the pressure apparatus for convenience, and proved satisfactory.

Operation

The puncture of the aorta was performed on the x-ray table. Lateral, oblique, and prone positions were investigated, and the most satisfactory was found to be the prone position. The patient's thighs and chest were comfortably supported by pillow padding. The puncture was made from the left side. Pentothal sodium intravenously was chosen for anesthesia because of its ease and simplicity of administration, and it proved to be very satisfactory. Most cases required less than 0.5 Gm. for the entire operation, although one patient received 2 Gm. without ill effect.

The actual puncture of the aorta is a simple procedure. While the area over the site of the puncture is prepared for aseptic technique, pressure cuffs are applied to each thigh as high as possible. This prevents a loss of the opaque solution to the lower extremities. Pressure of about 200 mm. Hg is necessary to constrict the circulation. When the patient is well anesthetized, the pressure cuffs are expanded. A needle with stylet is inserted into the spinal muscles three fingerbreadths from the spinous processes at the level of the lower border of the twelfth rib. The needle is directed superiorly and slightly medially. When contact with the body of the vertebrae is made, the needle is withdrawn slightly,

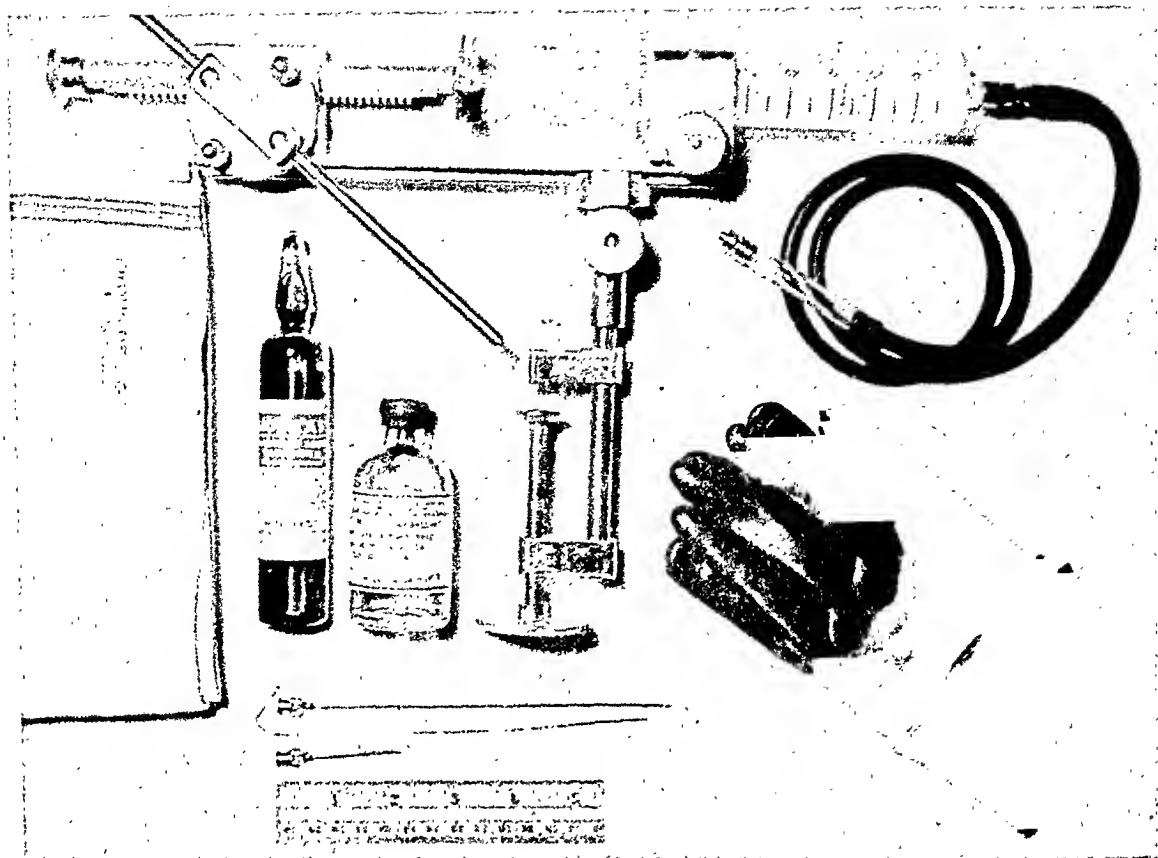


Fig. 1.—This illustrates the special equipment necessary for aortic injection. The pressure apparatus was made by the W. & H. Company for the injection of Pentothal. The needle is 18 gauge and 15 cm. in length.

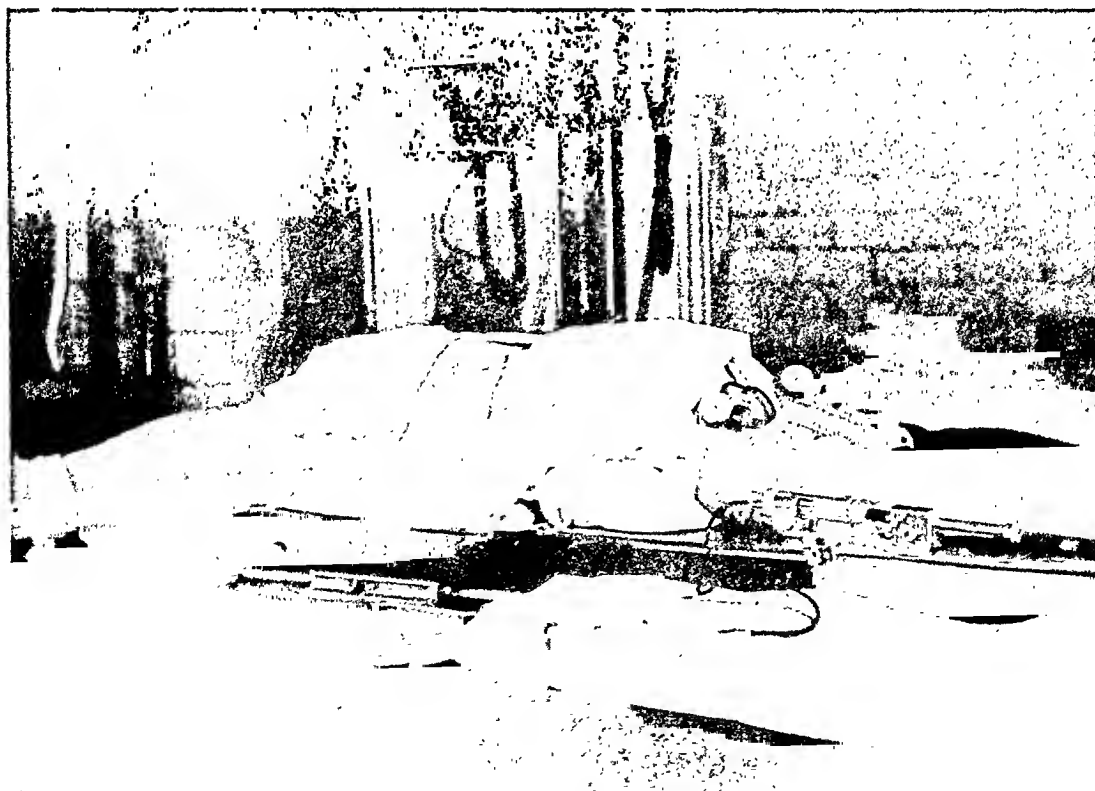


Fig. 2.—Illustration of the position of the patient found most satisfactory, with the pressure apparatus in position. The search plate should be taken before the administration of Pentothal. The preoperative setup should be complete before aortic puncture is made.

the stylet removed, and then directed slightly to the left or laterally. The actual puncture of the aorta can be felt and is evidenced by a flow of bright red blood. Actual pulsation of the flow is not always visible. It can be seen, however, within the glass bulb, when the pressure apparatus is attached. When the puncture has been made, the needle should be inserted further to a depth of 0.5 to 1 cm. When the operator is satisfied that the point of the needle is well



Fig. 34.—Search film using soft tissue technique.

within the lumen of the aorta, the pressure apparatus is attached, and 10 c.c. of sodium iodide (80 per cent) or at least 18 c.c. of Diodrast (70 per cent) are injected into the aorta over a period of about five seconds. Sodium iodide, when injected more rapidly, causes considerable irritation of the arterial bed, and a contraction of the uterus is observed frequently. Diodrast, unless injected at this rate, is not present in sufficient concentration to produce opacity in the x-ray plates. The first x-ray exposure is made as the injection is completed. A second exposure is made within an additional seven seconds. A longer delay usually produces unsatisfactory results.

X-Ray Technique

This procedure should be adaptable to any ordinary hospital x-ray equipment. The majority of satisfactory plates were obtained with a setting of 75 kilovolts, 200 milliampères, at 0.5 second with a high speed Bucky grid. A rotating anode tube was employed, and is considered desirable. The best plates by far were obtained with sodium iodide as the injected solution. Diodrast, while considerably less irritating, requires a greater concentration, and the outline of the vessels is not clear. There is need for a more satisfactory injectable opaque solution.



Fig. 3B.—Aortogram taken as the injection is completed. The maternal arterial circulation is outlined, and there is the characteristic mottling about the vessels which is probably the maternal sinuses of the placenta.

Postoperative Treatment

The anesthetic is withdrawn as soon as the injection is completed. After the x-ray plates have been exposed, the patient is immediately transferred to a cart, and the condition of the uterine musculature is observed, and the heart tones are checked at regular intervals. When the condition of the patient is considered satisfactory and the heart tones are normal, the patient is transferred to the division, and 1,000 c.c. of normal saline and 500 mg. of vitamin

C are given intravenously as soon as possible, in order to increase the rapidity of the excretion of the opaque solution. 100 mg. of Demerol has proved satisfactory to relieve pain and restlessness which may be present.

Complications

Extravasation of the injected solution was the most important complication encountered thus far. When this occurs, the solution has been injected into the adventitial tissue about the aorta, as shown by x-ray. Since the puncture

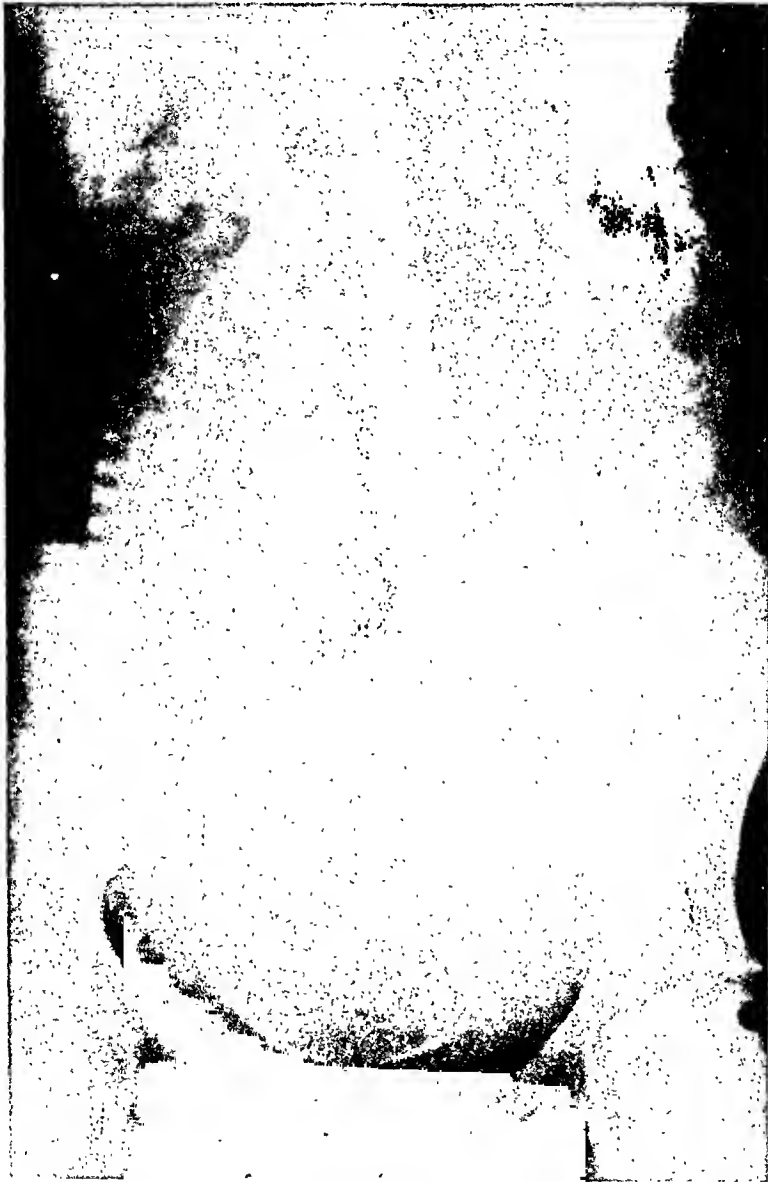


Fig. 3C.—Delayed exposure (10 plus seconds), showing the outline of the sinuses. No photographs in this article have been retouched.

is on the posteriolateral aspect of the aorta, it is logical that the extravasated solution will be retroperitoneal in every instance. Thirteen such accidents occurred in this series and, except for pain in the lumbar region for twenty-four to forty-eight hours, an elevation of temperature to 100° F. in two cases, for twenty-four hours, no ill effects were observed. Immediate evidence of extravasation is shown in the patient by hyperventilation and a catchy type of stertorous breathing which subsides after a few minutes. This is probably a result of irritation. The discomfort was controlled by 100 mg. of Demerol given

whenever necessary. X-ray plates taken at intervals showed the complete absorption of the solution in from twelve to seventeen hours. All patients in whom the procedure was successful were allowed to leave the hospital after

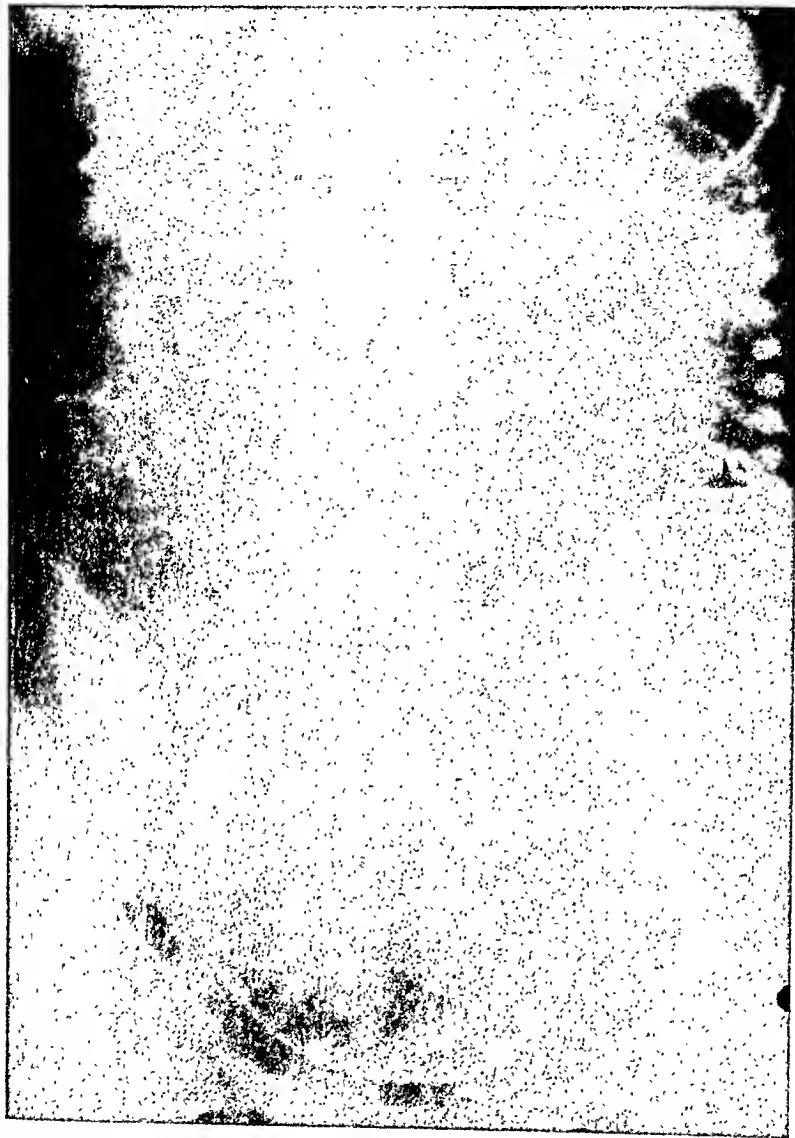


Fig. 4.—Characteristic appearance of the normally located placenta, showing the mottling about the maternal arteries.

eighteen hours. Those in which extravasation occurred were allowed to leave when the pain subsided, usually within forty-eight hours. Injection of a specific vessel, such as the left renal artery, celiac axis, hepatic artery, and the splenic artery, occurred during this investigation without ill effect. The first case attempted received the entire amount of the solution (15 c.c. 80 per cent sodium iodide) into the left renal artery, and, after four months of careful and complete observation, no pathological changes have been observed.

Postoperative Observations

Particular emphasis was placed on the observation of the behavior of the uterus after the injection. Sodium iodide is irritating to the intima of the arteries when the concentration is high. The first few cases in this series received

15 c.c. of this solution at a rapid rate, and, in these, a mild to moderate tetanic contraction of the uterus was observed, which began about one and one-half minutes after the injection and continued for five to eight minutes. During this time the fetal heart rate was counted as low as 76 per minute, rapidly returning to a normal rate, or above, shortly thereafter. This fall in rate in one case was considered physiological, as a result of the contraction of the uterus, rather than a reaction from the effect of the sodium iodide directly upon the fetus. Later,



Fig. 5.—This illustrates the implantation of the placenta in the region of the fundus and to the right.

when the amount of sodium iodide was decreased to 10 c.c. and the time of injection increased, thereby decreasing the concentration in the aorta, the contraction was slight and short in duration, and no marked change in the fetal heart rate was observed. Diodrast, when used, produced no evidence of irritation, and, therefore, no changes in the tonus of the uterus or changes in fetal heart rate were observed.

Early in the investigation, only patients at or near term were chosen. Many of these began labor immediately or shortly after the aortic puncture. However, as cases were selected with pregnancies of shorter duration, no incident of premature labor was encountered. All women in this series delivered

without mishap, and all babies were living and apparently unaffected. Mothers and infants were released from the hospital after the usual routine lying-in period.



Fig. 6.—The placenta is implanted in the region of the fundus and to the left.

Starch tests on the placentas were negative for iodide, and microscopic examination failed to produce evidence of damage to the chorionic villi. Whenever possible, the location of the placenta was determined manually after delivery, and, in each instance, when done, the location corresponded to that seen in the x-ray plates. One case of placenta previa came to cesarean section, and the location of the placenta was verified at the time of operation.

Discussion

There is need for a positive means of localizing the placenta. Bleeding during pregnancy is difficult to evaluate, and the decision for treatment is often made, necessarily, with no assurance of its correctness. This investigation was

devised, with the hope that it would offer a safe method as a diagnostic adjunct. When successful, it leaves no doubt as to the actual position of the placenta, and it eliminates the necessity for a vaginal examination.



Fig. 7A.—Search film taken of a patient at the twenty-eighth week of pregnancy. She entered the hospital because of a moderately severe hemorrhage.

Two cases of bleeding were encountered, one at the thirty-first week of pregnancy and the other at the twenty-eighth week of pregnancy. Aortograms were performed on these patients with no ill effects. There was no bleeding produced within 48 hours following the injection. The first patient was allowed to go to the thirty-seventh week of pregnancy before cesarean section was performed. The baby was lying in a transverse presentation and the location of the placenta was verified. The other case was allowed to progress to the thirty-eighth week of pregnancy and cesarean section was performed with successful outcome.

In both instances there was a question as to the cause of bleeding. If the bleeding had been produced by the separation of a low-lying placenta, the at-

tending danger to the mother and baby would be less than that bleeding which might be produced by an abruptio placentae. Since the hemorrhage, in both instances, was profuse and sudden in onset, gradually subsiding, the aortograms proved very useful when making a decision for treatment. In such cases, when consideration must be given to the viability of the baby, and a choice between



Fig. 7B.—Aortogram on patient (Fig. 7A) showing outline of maternal arteries over the lower segment. The characteristic mottling of the maternal sinuses is making its appearance below the fetal head. This is a case of central placenta previa, diagnosed at operation.

conservative and radical treatment is to be made, this should prove useful. In cases of profuse, unrelenting hemorrhage, when treatment must be instituted, it is certainly of no value. It becomes a question, at this point, whether the risks involved in aortography are worth while, in comparison with the hazards of watchful expectancy. While the results to this point have been satisfactory, and, even in the face of failure and extravasation, the patients do not seem to

have been harmed, I personally feel that the series is not large enough to come to a definite conclusion. The investigation will continue, and it is hoped that interest will be shown by others, in order to help improve the technique and to find a better injectable radiopaque solution. It appears evident that the procedure is sound, and the failures have been the result of errors in technique rather than a lack of fundamental soundness.



Fig. 7C.—This plate was exposed seven seconds after Fig. 7B, showing the solution remaining in the sinuses. The renal circulation is well outlined.

Summary

1. Aortograms were performed on 68 women during the later stages of pregnancy without serious complications.
2. When the procedure was successful, by delaying the time of the x-ray exposure, an outline of the maternal circulation over the placental site was visualized.
3. Two cases of placenta previa were encountered in this series.

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THE CHARACTERISTICS IN HYSTEROSALPINGOGRAMS IN TUBERCULOUS SALPINGITIS AND ENDOMETRITIS*

KO-CHI SUN, A.B., M.D., SHANGHAI, CHINA

I HAVE chosen the above topic for discussion, from the findings which are derived from the clinical material from the Woman's Hospital, Shanghai, China, since its opening on Jan. 17, 1935, to Jan. 9, 1947. They are not something new, nor do they represent experimental work, but they have appeared in our clinical routine to be of such a particularly unique and persistently constant picture that it is deemed worth while to put them on record.

In the literature, twenty-four contributions on hysterosalpingographic work have made reference to tuberculous salpingitis and endometritis. Two other authors wrote on the same subject but were uncertain of their own diagnoses, which were based merely by the presence of pulmonary tuberculosis in one¹⁸ and of tuberculosis of the hip joint in another.²⁴ In other words, not until one has on hand anatomic and/or bacteriologic evidences of tuberculosis of the organs affected, it would seem incorrect to make such a diagnosis. So much more so when all clinicians know that patients with tuberculosis elsewhere do not necessarily have the same disease in their genitals.

Of the twenty-four articles, only ten authors^{6, 14, 27, 26, 20 and 9, 25, 13, 10, 15, 16} published their x-ray pictures. Among them, the radiogram by Bond,² who alleged it to be shadows of calcium cast within the uterus and the tubes of a patient with appendicitis, was not a picture from injection of a contrast medium into the organs concerned. Thus, only twenty-seven published hysterosalpingograms of tuberculous salpingitis and endometritis are available for comparative description in the present study.

Since time does not permit any lengthy review or detailed description of the twenty-seven pictures obtained, suffice it to state here that the study of the topographic anatomy of the hysterosalpingograms is not an easy matter. It requires long experience and good judgment as to when the pictures are to be made, what contrast media to be used, and how the injection of the opaque material and the examination of the patient under the fluoroscope are to be practiced. Reuben Peterson has well expressed that it was easier to secure good plates than to interpret what the plates showed. Jameson even remarked in referring to tuberculous salpingitis and endometritis, "roentgenologically, pictures are very apt to be unintelligible or even worse, misleading." Both Gerlach and Madsen† concluded in their hysterosalpingographic work to have found no specific picture of the tuberculous changes. Neither did Schultze nor Kjehlberg point out in their voluminous monographs on the subject any characteristic features of tuberculous salpingitis and endometritis.

*Abstract of an address, by invitation, of the guest speaker at the Seventieth Annual Meeting of the American Gynecological Society, Seignior Club, Montebello, Quebec, June 17 to 19, 1947. For lack of space, only a portion of this address can be included in our pages.

†Since writing this article in June, 1947, the author had the pleasure to visit with Prof. Rydberg in Copenhagen, and learned from Dr. Madsen that he was about to publish his newer findings in his hysterosalpingographic work on tuberculous salpingitis and endometritis in November, 1947.

In my study of the twenty-seven hitherto published hysterosalpingograms of tuberculous salpingitis and endometritis, Robins and Shapira appeared to be the first to recognize some of the peculiar roentgenologic features of the disease, while Magnusson added many more and elaborated them into great details. In Magnusson's own words, the "finely jagged and ragged contours with small lumen defects and sometimes with abscess and fistula-like dilatations of the tubal lumen constituted the roentgenologic signs of tuberculosis." However, when one comes to review the twenty-seven pictures which I have at hand, one can point out many more characteristic features which the ten authors did not mention in their own descriptions. To be brief, three distinct and constant features have been found in common in all of them. First, the shadows show defective nonhomogenous filling of the contrast medium. Second, the tubes appear like thin stiff wires with irregular sacculations toward the fimbria. In the third place, in no case is there any free contrast medium in the peritoneal cavity. But, these are by no means all the points in the hysterosalpingograms in tuberculous salpingitis and endometritis, as I shall now point out in my own present observations.

Personal Observations

The present observations were obtained from six patients of 138 who had hysterosalpingograms in the Woman's Hospital during the period mentioned. All the six patients had two things in common. All came for sterility. All came during the silent stage of tuberculosis. All the x-ray tests were made by the author personally in order to secure the uniformity of technique and the complete removal of the element of individual variations in the evaluation of the tests. The eleventh day of the menstrual cycle was chosen for the test in all cases. The oil of lipiodol was the contrast medium. Very slight pressure was used to inject the oil. The injection was done under the fluoroscope. One cubic centimeter was employed for each injection according to the so-called "fractional method" of Joachimovitz and Hyams. During and after each injection, the hand was run over the suprapubic region with up and down movements in order to see the rise and fall of the shadows, the contractions and changes in the shape of these shadows, as well as their positions. At the same time, the patients were moved from side to side as well as obliquely so as to obtain a lateral or oblique view of the organs so filled by the contrast medium. Films were taken whenever necessary, and a plain film was always made before and twenty-four hours after the injection.

The accompanying illustrations are from the representative films made on the six patients upon whom the diagnosis of tuberculous salpingitis and endometritis was fully established. All six patients had operations; all operative specimens showed typical tuberculosis without any other disease; and in all cases animal inoculations from the operative material were made, although in only one did the animals show evidence of tuberculosis. In this patient, a positive culture of the tubercle bacillus was also obtained from the operative material.

Inasmuch as space does not permit a full description of all the films here, suffice it to summarize the salient features in a general way. First, in the plain films made before the injection of the contrast medium in four (Cases 1, 2, 3 and 4) of the six patients, x-ray opaque bodies were seen in their pelvises. In Case 2, the shadow persisted even after a laparotomy. In Cases 2 and 3, fibrocalcereous adhesions were visible. Second, the filling of the uterine organ and the tubes was rather tardy. In the process of filling, no sign of con-

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tractions was apparent. When filled, the cervical canal exhibited a fuzzy shadow which has been described "manelike" or "feathered" by various workers. The uterus appeared like a trumpet or a Voorhees' balloon, and its borders were shaggy and jagged. Its fundic shadow was invariably convex, and its lateral contour, likewise, bulging. The tubes, if filled, were filled in a jerky, fragmentary fashion so that their entire contour appeared to be beaded, segmented, and "fractured." They were stiff, wiry, thready, and drooped downward like a filament. There was often an abrupt ending of the filling process. The fimbria were pouchlike, saccular, and diverticular in shape. In the third place, the appearance of the entire contrast medium was uneven, nonhomogenous and simulating foreign bodies. Next, the stationary manner or the lack of spread of the contrast medium in the free peritoneal cavity and the frequent complete emptying of the filled tubes after twenty-four hours were quite characteristic. Last, as seen in Case 3, the imperfect filling of the organs might mislead one to think of a hypoplastic or a malformed uterus.

We may now pause for a moment in order to see just how such characteristic features in these hysterosalpingograms are produced. One must first remember that a hysterosalpingogram is but a shadow of the hollowed spaces (cavity or lumen) of the female internal genitals, and that the characteristics in the shadows are produced from the characteristic anatomy of these hollow spaces. Normally, the inner surfaces of these hollow spaces are lined by soft and distensible mucous membranes. They may be wrinkled but become smooth when give rise to clear-cut and sharply outlined shadows in conformity with the shape, size, and position of the parts. These parts are muscular in nature and capable of movements or contractions by their tonicity. This tonicity may vary with the cyclic phases of menstruation. In other words, the shadows would exhibit not only the clear smooth and sharp outlines, contractile waves, and even thickness of the hollowed spaces, but also the rhythmical propagation of the contrast medium within the spaces. Any change or deviation from the normal must have come from a distinct pathologic process, namely, the disease of tuberculosis under present discussion.

As we all remember, the commonest mode of tuberculous invasion is by the blood stream. One must refer to Lisfranc for the pathologic anatomy of the tuberculous uterine cervix and to Kiwisch, that of the Fallopian tubes. Of late, Sutherland, Sharmann, Rubau, Eichner, Auerbach, and others have added considerable contributions to our knowledge on the subject. Speaking briefly the initial tuberculous bombardment is on the musculature of the tube, the commoner organ affected, or of the tube, or of both. Then, the foci of suppuration spread both ways to the mucous membranes and to the serosa. The route of spread appears to be mostly from tube to cervix and, within the tube itself, from fimbria to uterine cornua. The process is what Schramm and Simmonds called a bacillary catarrh. The mucous membrane is covered with thick ulcerative pads of caseation and, if old, partly organized and even calcified masses. Within the tube, this process does not develop evenly throughout its entire length. The abdominal end is more exudative, while the middle portion, patched with fibrin and the uterine end, studded with nodules. Thus, the tubal sphincters have become more prominent. The fimbria is occasionally open, but the ostium is closed. Hence the tubal lumen is essentially a passive way with the vegetations, the papillary excrescences and the organized granulation tissue protruding into it, which makes the passage of the contrast oil difficult. The x-ray shadow of such a passage is naturally stiff and wiry and, therefore, shows defective and nonhomogenous filling. When progressive caseation of the walls of the organ breaks through the serosa, they are studded with similar foci of fibrous and calcareous deposits. The stiffened organ becomes the so-called "uterus sclereau."

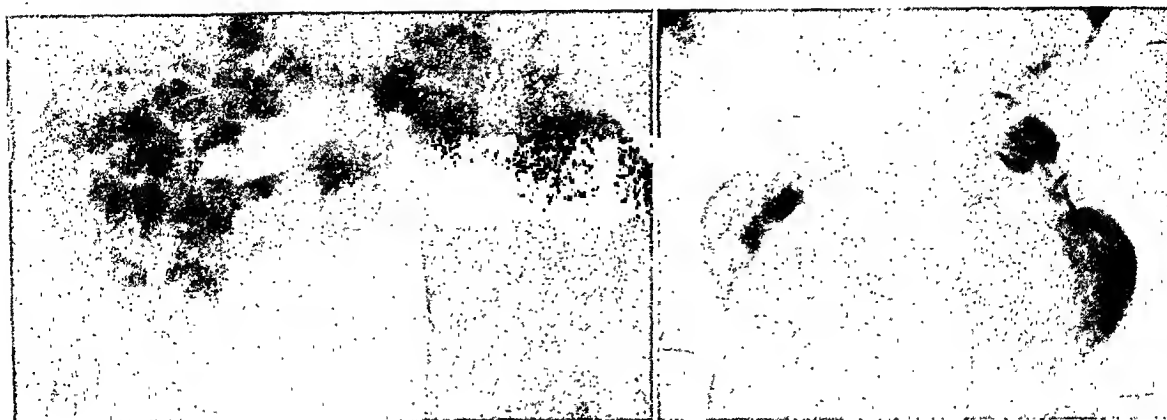


Fig. 1.

Fig. 2.

Fig. 1.—Case 1. (No. 1349) A-P view after injection of 3 c.c. lipiodol.

Fig. 2.—Case 2. (No. 1385) A-P view after injection of 3 c.c. lipiodol.

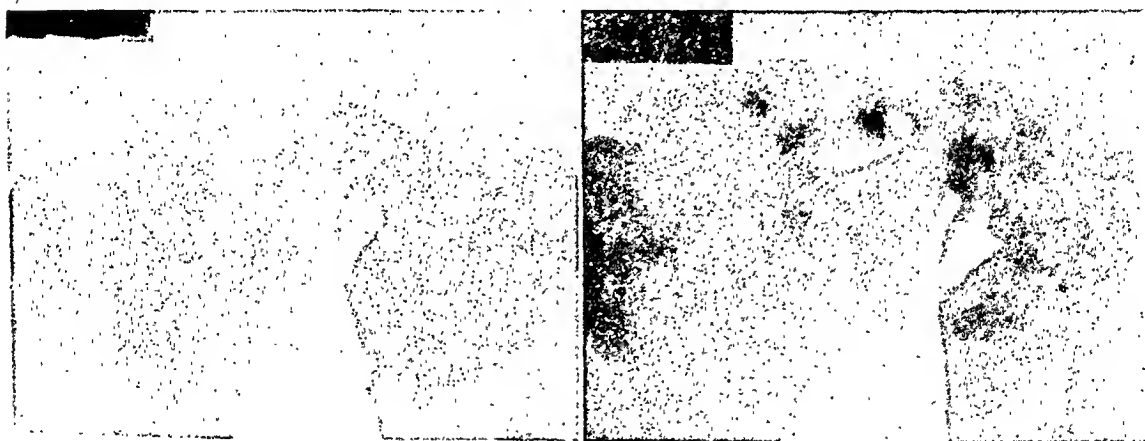


Fig. 3.

Fig. 4.

Fig. 3.—Case 3. (No. 2311) A-P view after injection of 2 c.c. lipiodol. (First test.)

Fig. 4.—Case 3. (No. 2311) A-P view after injection of 3 c.c. lipiodol. (First test.)

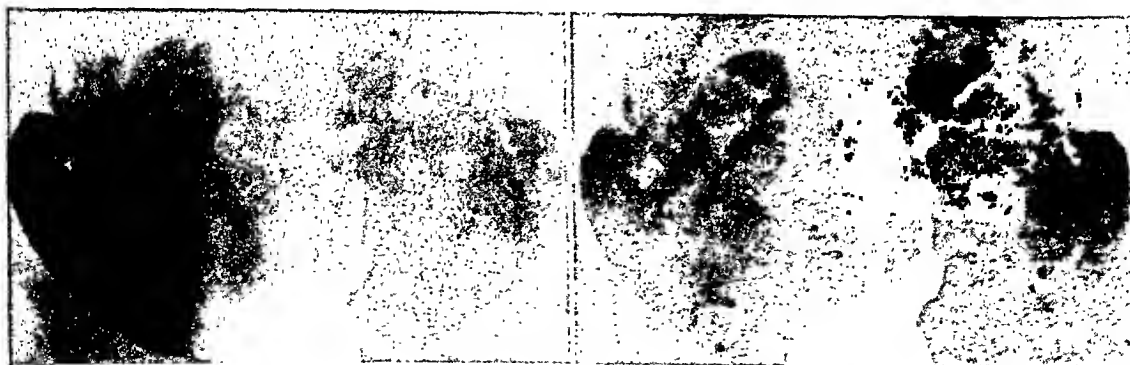


Fig. 5.

Fig. 6.

Fig. 5.—Case 3. (No. 2311) A-P view after injection of 2 c.c. lipiodol. (Second test.)

Fig. 6.—Case 3. Another view taken five minutes after Fig. 5.

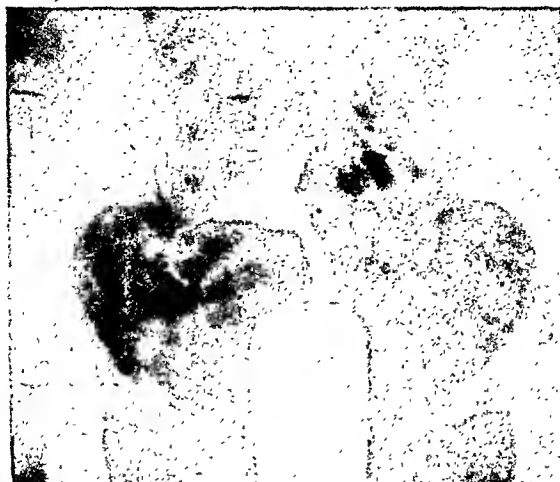


Fig. 7.—Case 4. (No. 2415) A-P view, after injection of 3 c.c. lipiodol.

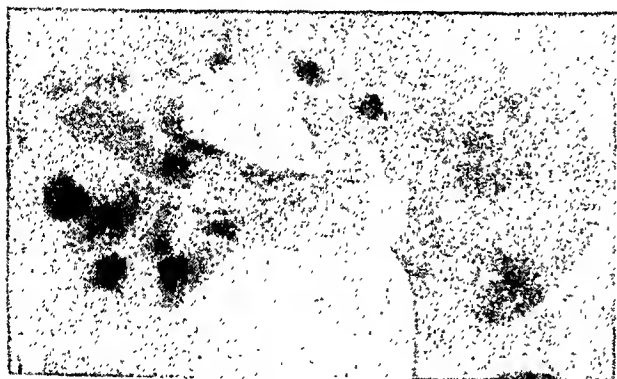


Fig. 8.

Fig. 8.—Case 5. (No. 3400) A-P view after injection of 1 c.c. lipiodol.

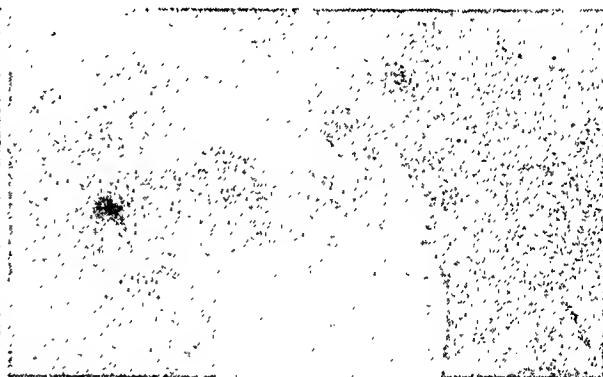


Fig. 9.

Fig. 9.—Case 5. (No. 3400) A-P view after injection of 2 c.c. lipiodol.



Fig. 10.—Case 6. (No. 3431) A-P view after injection of 2 c.c. lipiodol.

With these pictures in mind, one can easily understand why the contractility of the musculature of these organs has diminished or disappeared. Either the nerve elements have been injured, or the stiffened state of the muscles with numerous projecting masses of tuberculous tissue beyond the surface of mucous membranes has rendered the muscles mechanically impossible to contract. Such masses may thus hold and retain the contrast oil in the uterus even after a menstrual flow and after a biopsy curettage (Case 2).

Microscopically, one is struck by the absence of agglutination of the mucous folds. Slight adenomatous proliferation of the mucosa makes the lumen thready and filamentous. Thus, the not infrequent patency of the tubes will, therefore, explain the rare occurrence of pregnancy in either tube or uterus as reported by Stevenson and Wharton, Busby and Fischer, Schroeder and Rau, and others.

Differential Diagnosis of Hysterosalpingograms

The study of hysterosalpingograms cannot be complete without a sketch of an outline in making a differential diagnosis of a hysterosalpingogram that is representative of tuberculous salpingitis and endometritis from one that is indicative of other conditions. The former studies of Guthmann and Staehler, Menees and Miller, Philipp and Huber, and Hyams have unfortunately failed to include the tuberculous and the normal in their publications. However, one cannot emphasize too strongly that the task must rest upon a radiologist and a gynecologist for well co-ordinated thought. In this connection, not only a precise clinical history and many technical points are important, but one must also remember that the uterine cavity and the tubal lumen are potential spaces. The linings of these spaces are different on different days of a menstrual cycle and in different regions. The injuries produced on them by diseases are variable. So, it may not be out of place to describe first a normal hysterosalpingogram on the eleventh day of the menstrual cycle, and then to compare it with those in other affections.

1. *Normal hysterosalpingogram.*—The findings in a normal hysterosalpingogram depend not only upon the age of the patient, but also on which cyclic day of menstruation the picture is made. When the endometrium is not completely healed after a menstruation, the oil injected may easily enter the veins. As pointed out, the day usually chosen for the work is the eleventh day. Here, the cervix is well filled like the shape of a smooth spindle. The uterus appears to be triangular with slight concavity over the fundic region, slight annular constriction at the site of Bandl's ring, with smooth, well-outlined and clearly cut borders. Both uterine cornua are pointed, with their sphincters shown or not shown. The shadows of the tubes on each side are seen to be composed of three segments: a horizontal straight line in their interstitial portion, a descending oblique and somewhat wavy line over their middle portion and a wavy ascending erectile line at their ampullary ends. Not infrequently, the ampulla of one tube is seen to curve around the corresponding ovary and to be applied quite closely, exhibiting the so-called "*ovaria fossa Stellung*." The contrast medium enters the free peritoneal cavity by the uterine and the tubal peristaltic action without any effort, and spreads over it like the paint brushed over a surface by the painter.

2. *Hyperplasia.*—Here the mucosa is thick and festooned into folds. When only a small amount of the contrast medium is injected by the fractional method, there are linear lines in the uterine cavity, as the micrographic work of Defrensne and of Raisz has amply demonstrated. Even the extreme enlargement of the mucosal folds would not show uneven, nonhomogenous shadow and there is no loss of the smooth outlines of the borders of the organ.

3. *Hypoplasia.*—Everything normal except in a diminished size. The tubes may be unusually long and somewhat wavy due to fetal convolutions. How-

ever, one should not confuse hypoplasia with tuberculosis of inner genitalia. Merletti found 28 tuberculous uteri in 80 hypoplastic patients. According to Heyneman, hypoplastic uterus predisposes localization of tuberculosis in the organ. But Sellheim appeared to be more reasonable in claiming that atrophy of the uterus is secondary to tuberculosis.

4. *Polypi and Submucous Myomas*.—Unless these lesions have become degenerated into a malignant condition, they usually give rise to well-outlined smooth and clear-cut shadows with ovoid, circular or elliptical contour according to the shape of the tumor. The tumors are invariably surrounded by the contrast medium. So, different films must be made in different positions.

5. *Retained Products*.—Retained products in the uterine cavity such as placental cotyledons are shown in the x-ray picture, according to Cotrim, resembling polypi or submucous fibromas. The intracavitary outlines may not be so smooth and the uterine cavity itself is slightly ovoid and large. The condition must not be confused with cancer. The clinical history in each is different.

6. *Ectopic Pregnancy*.—With decidua in situ, Mathieu has described the characteristic notched or toothlike outlines along the fundic region. But, a carefully taken history together with bedside picture of the patient is more important than an x-ray film.

7. *Endometriosis*.—The x-ray picture of endometriosis has been extensively studied by numerous workers. The peculiar feature here is the continuity of the mucosal lumen into numerous ramifications in the walls of the uterus or tube, or both. The contrast medium enters into these crevices to give rise to a picture like the roots of a plant or what Phillipp and Huber called "spitzer Zaeken." As Madsen of Copenhagen has pointed out, there is a network of numerous pinhead-sized spots or of fine small threadlike channels leading from the main lumen. They look like venous channels, for they end within the musculature of the organ. Åkerland, too, showed the diverticular crypts and lacunar excrecences deep in the musculature. But none has any connection with the pelvic venous system. What Buteler compared this endometriotic picture to be more or less similar to that of tuberculosis is erroneous.

8. *Adenomyosis*.—It is not uncommon for chronic infection and adenomyosis to coexist in a uterus. Since tuberculosis is a form of chronic infection, some confusion has existed. With adenomyosis, the organs are naturally large. The uterus is irregularly deformed due to irregular distribution of the growth. Its contour is bulging but the outline is smooth. Also dots and diverticuli are present.

9. *Cancer*.—The clinical history is most important. If early, there is a localized narrowing of the cavity or lumen; then, elongation and enlargement. When craters and ulcerations occur, the margins are more irregular and elevated. There are small crevices. This is what Gerin-Lajoie called the crenated and fongous shadow.

10. *Calcified Shadows Other Than Tuberculosis*.—Numerous authors have called attention to the presence of opaque shadows in the pelvic cavity that are not necessarily tuberculosis. Stones in the ureters and bladder, teratoma, dermoid tumor, calcified fibroma, etc., are examples. Still many do not look for these things chiefly because they are not there clinically. In 1932, Bârcă described and called attention to the significance of radiopaque consolidation or even calcification in the Fallopian tubes. Therefore, it is always advisable to take a plain film first and to examine the patient after the injection in all directions so as to locate the position of such shadows.

11. *Chronic Endometritis and Salpingitis Other Than Tuberculosis*.—Other chronic infections of the uterus begin in the endometrium first. They do not alter so much of the muscular wall as the mucosa. Even affected, the mucous lining remains smooth. The cavity or the lumen may become widened and festooned.

12. *Malformation, e.g., uterus bicornis*.—This condition has given rise to much confusion with tuberculosis of the uterus and tubes. It is equally symptomless as many of the tuberculous cases. A casual examination of the x-ray films does not give much information. But, a bicornuate uterus should show two distinct shadows, complete or otherwise, of the uterine body as Rossi demonstrated. Their outlines and contours are smooth and free from any intracavitary irregularity or defect. The contrast medium remains homogenous. However, tuberculosis does exist in a malformed uterus as in the two cases of Brandess who also reported the co-existence in a case of malformed uterus of both tuberculosis and myoma. On the other hand, genuine tuberculosis of the tubes and uterus has been mistaken very frequently for uterus bicornis, as in the case of Martineau (his Fig. 7), Nahmmacher (his Fig. 16) and Magnusson (his Cases 8 and 10), as well as my own observation in Case 3. The contributions of Colloridi and Rouchy have discussed the topic in great details.

Summary

To summarize, unique and fairly constant topographic characteristics are seen in the hysterosalpingograms in tuberculous salpingitis and endometritis. Their pathogenesis has been speculated. An outline of differential diagnosis of hysterosalpingograms in various diseases has been presented. The presentation does not mean that all cases of tuberculous salpingitis and endometritis would present all the characteristics in their hysterosalpingograms. Never should it carry the idea that tuberculous salpingitis and endometritis be diagnosed by the x-ray pictures alone. It is hoped that the work may be done a little more frequently and extensively so that we can learn more out of it.

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AN EVALUATION OF PLASMA PITOCINASE DETERMINATION IN THE TOXEMIAS OF PREGNANCY*

GLORIA T. ARAGON, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

THE marked response to posterior pituitary hormone administration associated with the toxemias of pregnancy has been demonstrated.¹⁻³ The explanation of this phenomenon, however, like the cause of the toxemia itself, is unknown. Various workers have speculated as to the etiology of toxemia on the basis of either an increased secretion of the hormone or its ineffective inactivation and destruction in the body. Hofbauer (1918) was the first to relate an abnormal secretion of the posterior pituitary with the etiology of eclampsia and pre-eclampsia. This author later postulated the ineffective destruction of the posterior pituitary hormone by acetylcholine, resulting in the relative increase in the blood of the former.² The recovery of an antidiuretic and pressor substance in the blood of pre-eclamptic and eclamptic women by Anselmino and Hoffman⁴ gave further emphasis to this relationship. Unfortunately, subsequent studies on this posterior pituitary-like substance by other investigators showed conflicting results.⁵⁻¹⁰

Recent work points to an enzymatic destruction of the posterior pituitary hormone by various tissue extracts (intestine, liver, kidney, muscle), as well as by dog, rabbit, and human blood.¹¹⁻¹³ The quantitative difference in the degree of inactivation of this hormone by nonpregnant and pregnant human sera was probably first suggested by Küstner,¹⁴ who also stated that there was an increase of the hormone in serum of eclamptic patients. Von Fekete in 1932¹⁵ likewise made the observation that pregnancy serum, as compared with the nonpregnant, showed increased inactivation of the hormone. A detailed study of the enzymatic nature of this hormone inactivator in serum and its increase with the age of pregnancy was reported by Werle and co-workers.^{16, 17} Woodbury, et al.,¹⁸ by the use of intrauterine pressure recordings in patients, confirmed these previous studies but did not find any quantitative difference between the neutralizing power of toxemic and normal pregnancy blood.

Page^{19, 20} has devised a quantitative bioassay for a substance he named "pitocinase," which presumably is responsible for the enzymatic destruction of the posterior pituitary hormone. This substance, though not yet chemically isolated, has all the characteristics of an enzyme.

The present study was undertaken to determine whether there was any significant relation between the plasma pitocinase, and the diagnosis and prognosis of the toxemias of pregnancy.

*Supported in part by the Chicago Lying-in Hospital Fiftieth Anniversary fund for Research on Eclampsia.

Method and Results

All plasma pitocinase determinations were obtained according to the methods and calculations reported by Page.^{#19-21} Pitocinase values as reported by Page have been considered as "normal," and our results are listed as either normal or low in comparison.

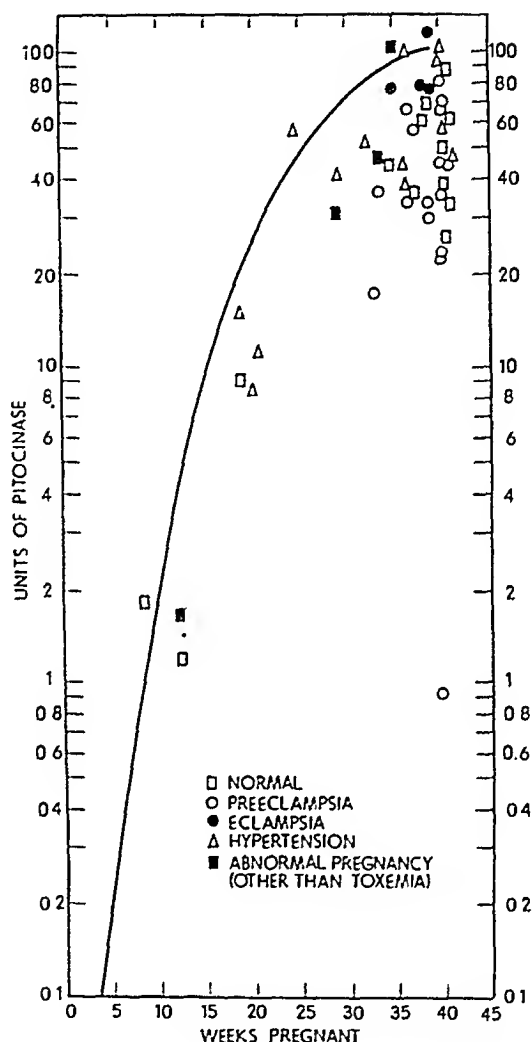


Fig. 1.—Pitocinase levels (compared with Page's curve).

A total of 50 pregnant patients (33 with toxemia) were studied. On a select group of patients, repeated determinations (two to four) were made at several days' interval, making a total of 83 pitocinase assays. Table 1 illustrates the results obtained. Figs. 1 and 2 show our values plotted against the pitocinase curve reported by Page. No attempts were made for pitocinase determinations in very early pregnancy, inasmuch as the main interest in the present work was the correlation of pitocinase levels with toxemia rather than as diagnostic of pregnancy. There was only one case studied of early pregnancy of eight weeks, and in this case a normal value was obtained.

The pitocinase levels obtained follow the pattern of Page. In general these values are lower than those he reports. In only three instances out of the 83 determinations did our values exceed the previously reported levels by 10

*Details in the technique were taken up in personal communication with that author.

TABLE I. PLASMA PITOCINASE LEVELS

DIAGNOSIS	TOTAL	SAME VALUES*	LOWER VALUES*
Normal pregnancy	13		
first half	3	2	1
second half	10	1	9
Pregnancy complicated by:			
diabetes insipidus	1	1	
placenta previa	1	1	
pyelitis	1	1	
hyperemesis gravid.	1	1	
Toxemias of pregnancy	33		
eclampsia	4	4	
pre-eclampsia	17	4	13
hypertension	12	4	12
Total	50	19	34

*Values compared with those reported by Page.^{10, 20}

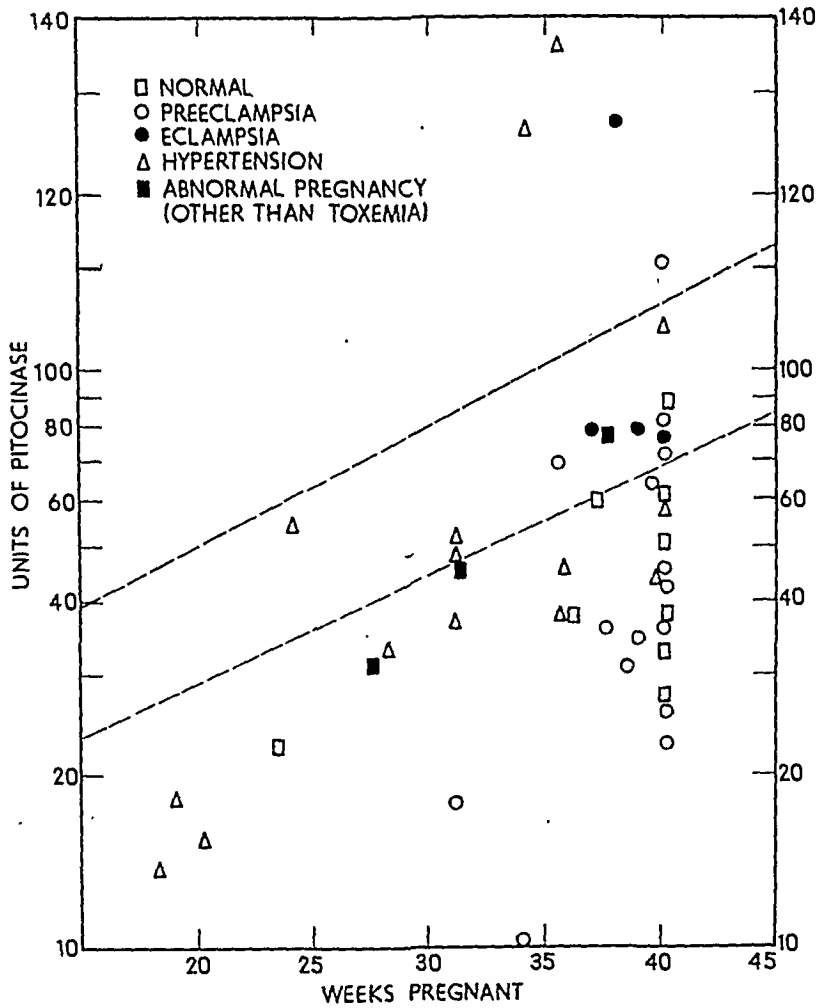


Fig. 2.—Pitocinase levels in the second half of pregnancy.

per cent (one eclamptic, one hypertensive with subarachnoid hemorrhage, and one with mild hypertension associated with erythroblastosis). As has been pointed out by Page, there is a wide variation of values in the toxemias without any significant difference between hypertensive and pre-eclamptic patients.

The levels in individual patients, as shown by repeat determinations, fluctuate without apparent relation to the clinical course of the patient. This is illustrated in Figs. 3 and 4.

Of the 33 toxemia patients studied, 21 were subjected to the pituitrin test as described by Dieckmann and Michel,¹ and the results of this test were correlated with the pitocinase levels, Table II. Samples for pitocinase determination were taken before the pituitrin test was done. In four of the patients who

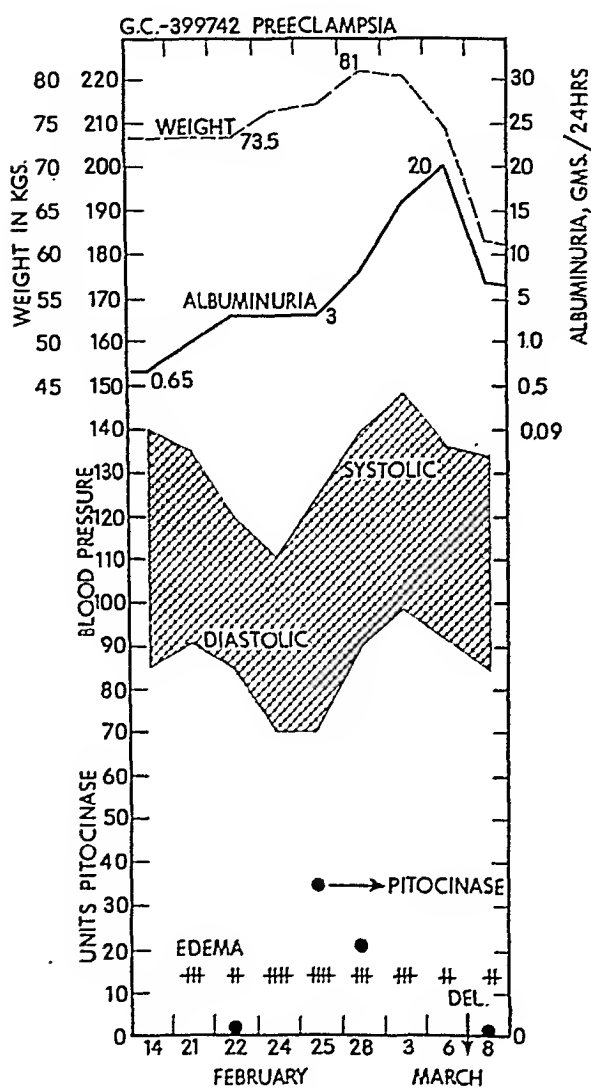


Fig. 3.

Fig. 3.—The pitocinase determinations (black dots) show no correlation with the clinical condition of the patient with pre-eclampsia.

Fig. 4.—The pitocinase determinations (black dots) show no correlation with the clinical condition of the patient with hypertensive toxemia.

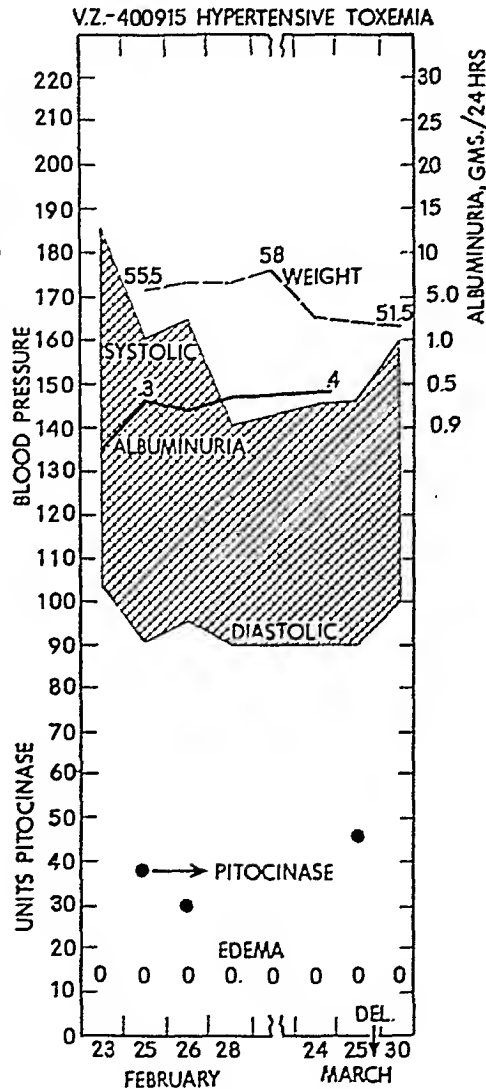


Fig. 4.

showed a marked rise of blood pressure with the pituitrin test, a pitocinase assay was repeated within an hour after the test. Three of these patients gave lower repeat values and one showed an increase.

It is interesting to note that all the four eclamptic patients studied showed high pitocinase values, whereas pre-eclamptic and hypertensive patients gave lower and more scattered values.

TABLE II. A COMPARISON BETWEEN THE PITOCINASE LEVELS AND THE RESPONSE TO THE PITUITRIN TEST*

DIAGNOSIS	NO. OF CASES	POSITIVE TEST	PITOCINASE		NEGATIVE TEST	PITOCINASE	
			NORMAL†	LOW†		NORMAL†	LOW†
Eclampsia	1	1	1	0	0	0	0
Pre-eclampsia	15	8	2	6	7	2	5
Hypertension	5	1	0	1	4	1	3
Total	21	10	3	7	11	3	8

*Dieckmann and Michel.¹†Values compared with those of Page.^{19, 20}

Discussion

There is sufficient evidence to suggest an enzymatic destruction of the posterior pituitary hormone in the human body. "Pitocinase" may well be that enzyme. As an organic catalyst, pitocinase, while accelerating the destruction of the hormone, should, ideally, be neither destroyed nor altered and should catalyze more than 200,000 times its weight of reacting material.²² The results of the present study show that the pitocinase levels, in the toxemias of pregnancy, are not of any diagnostic or prognostic value. It seems that the hypersensitivity shown by pre-eclamptic and eclamptic patients to the posterior pituitary hormone is independent of plasma pitocinase levels. These findings are in accord with Woodbury, et al.,¹⁸ who claim that normal pregnant as well as toxemic patients can rapidly inactivate pitocin and pitressin and that the hypersensitivity of the pre-eclamptic and eclamptic patients to these hormones is not due to a diminished ability to inactivate these substances. It is likewise reasonable to suppose that there is an optimum level of pitocinase for maximum destruction of pitocin, above which no further acceleration in the neutralization of the hormone takes place. The increase of pitocinase levels with the age of pregnancy may therefore be entirely unrelated to the sensitivity of certain pregnant patients to the posterior pituitary hormone.

Determinations for presence of an antihormone^{22, 23} in normal pregnancy may explain the increased inactivation of solution of postpituitary by normal pregnancy serum. Further investigation into the various other enzyme systems during normal and toxemic pregnancy may uncover knowledge concerning their metabolism, and might even result in a diagnostic and prognostic guide for the toxemic state.

Summary and Conclusions

1. A total of 83 pitocinase determinations were made on 50 pregnant patients, 33 of whom were toxemic.
2. The enzymatic nature of the pitocin inactivation by pregnancy serum was confirmed.
3. In general, the range of pitocinase values obtained followed the curve reported by Page.
4. There is no significant difference in pitocinase values in hypertensive and pre-eclamptic patients. In both there is a wide range and a scatter of values.

5. No correlation was found between the pitocinase levels, and the clinical course of the toxemia and the hypersensitivity of the patient to pituitrin, as determined by the pituitrin test.

6. It is, therefore, concluded that plasma pitocinase levels in the toxemias of pregnancy are of no prognostic or diagnostic value.

I am indebted to Dr. Wm. J. Dieckmann for suggesting this problem and for making facilities available.

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LEUCEMIA AND PREGNANCY*

JOHN A. WILLIAMS, M.D., PHILADELPHIA, PA.

*(From the Division of Obstetrics and Gynecology of the Pennsylvania Hospital,
The Philadelphia Lying-In Hospital)*

FORTUNATELY, the coexistence of leucemia and pregnancy is rare. Me-Goldrick and Lapp,¹ reviewing the literature in 1943, cited 80 instances (including one of their own) with statistical evaluation of available data. Since that time I have been able to find 8 more reports, all of which seem sufficiently well authenticated to warrant inclusion in this study, which has as its purpose the presentation of two patients (with autopsy findings in one), review of reports since the last survey, and a few summary remarks concerning prognosis and management of this condition.

Presentation of Patients

CASE 1.—A 27-year-old primigravida housewife consulted Dr. F. S. Dunne on June 22, 1945. Her last menstrual period was Feb. 12, 1945, and the expected date of confinement was Nov. 19, 1945.

Except for recurrent attacks of pyelonephritis for the previous 16 years, her past history was irrelevant. In the three months prior to the last menstrual period she had lost 40 pounds in weight, but had noticed no unusual symptoms. She claimed that she was sensitive to procaine, cocaine, morphine, codeine, aspirin, sulfonamides, and barbiturates.

Physical examination revealed no abnormalities except for moderate pallor of the oral mucous membrane. The uterus was enlarged to 5 cm. above the symphysis pubis. The liver and spleen could not be palpated and there was no evident lymphadenopathy. The pelvis was of gynecoid type and was considered adequate for vaginal delivery. The blood Wassermann and Kahn reactions were negative. The hemoglobin value was 64.8 per cent (10.0 Gm.), red blood count 3.8 million, the white blood count was not done.

Despite progressive weight loss (a total of eight pounds during the period of gestation) she remained well until mid-August and mid-September when she had febrile episodes of pyelonephritis which responded adequately to courses of mandelic acid.

On Oct. 10, 1945 when she was admitted to the hospital she was having pains every five minutes which produced no cervical dilatation and which soon subsided. Examination of the blood done before discharge from the hospital the following day revealed a hemoglobin value of 71.4 per cent (11.3 Gm.); red blood cells, 3.4 million; and white blood cells, fifty thousand, two hundred.

The high leucocyte count was confirmed by a second examination on Oct. 15, 1945, which gave results indicative of chronic myelogenous leucemia, i.e., white blood cells 102,000 with promyelocytes 2 per cent, myelocytes 5 per cent, metamyelocytes 9 per cent, stab forms 20 per cent, segmenters 56 per cent, lymphocytes 5 per cent, eosinophiles 1 per cent, basophiles 2 per cent; platelets

*Presented at a meeting of the Obstetrical Society of Philadelphia, April 3, 1947.

were abundant, and an occasional nucleated red cell was encountered. On this date there was no lymph node enlargement and no evidence of hemorrhagic or purpuric tendency. Because of the advanced pregnancy palpation was difficult and neither the liver nor the spleen could be felt, but the latter organ seemed to be moderately enlarged to percussion.

On Nov. 2, 1945, she was readmitted to the hospital, and the following day, sixteen days before the expected date of confinement, she was delivered of a living normal female infant (wt. 6 pounds 2 ounces) by elective cesarean section under gas-oxygen-ether anesthesia. Although no troublesome bleeding or oozing was encountered, she was given 500 c.c. of citrated whole blood during the operation. The spleen was palpated while the abdomen was open and judged to be 2 to 3 times the normal size.

The placenta measured 16 by 13 by 5 cm. and weighed 550 grams. Microscopic examination of the placenta showed numerous small areas of calcification throughout, and crowding of the sinusoids with small immature polymorphonuclear leucocytes, but no abnormal cells could be found in the fetal placental circulation.

The postoperative course for both mother and infant was uneventful. The infant showed no evidence of blood dyscrasia and weighed 5 pounds 14 ounces, when both were discharged from the hospital on the twelfth postoperative day.

On follow-up examination Dec. 7, 1945, the spleen was found to be enlarged to 7 cm. below the left costal margin; there was no detectable hepatomegaly, lymphadenopathy, or bleeding tendency. The patient stated that she felt very well. At that time the hemoglobin value was 69 per cent (10.7 Gm.), red blood cells 4.0 million, and white blood cells 72,000 with promyelocytes 3 per cent, myelocytes 10 per cent, metamyelocytes 14 per cent, stab forms 33 per cent, segmented forms 30 per cent, lymphocytes 6 per cent, eosinophiles 4 per cent; platelets were abundant.

General supportive measures and the one blood transfusion given at operation comprised the therapies employed.

Shortly after the follow-up visit in December the patient moved from Philadelphia. The details of her present status are not available, but both mother and child are reported to be doing well—one year after delivery. The mother is, in fact, pregnant again.

The following case is, to my knowledge, unique as the first reported instance of monocytic leukemia associated with pregnancy.

CASE 2.—A 35-year-old white para i, gravida i, housewife, seven months pregnant, was admitted to the Pennsylvania Hospital on April 30, 1946, because of hypertrophied gums, swelling of the neck, and mild sore throat. Her last menstrual period commenced Sept. 23, 1945, and June 30, 1946, was the expected date of confinement.

The present illness ostensibly began one month before admission when, shortly after the breaking of a decayed left upper third molar tooth, her gums rather abruptly became swollen and tender, and bled easily. With the persistence of these symptoms and the onset of tender submaxillary swellings, she was admitted for study and treatment.

Other than the usual childhood diseases, "virus pneumonia" in October, 1945, and an exacerbation of a chronic sinusitis with the present illness she had always enjoyed excellent health, and this pregnancy had been uneventful. Her previous pregnancy had ended with a cesarean section at term for placenta previa.

The physical examination revealed a well-developed and well-nourished woman in no apparent distress. The temperature was 100.8° F., pulse 120, respirations 18, and the blood pressure 122/ 76. Aside from moderate pallor the skin was not remarkable; there were no petechiae. The mouth disclosed pale mucous membrane, induration and swelling over the hard palate and the floor of the mouth, foul breath, and marked generalized tender hypertrophy of the gums on both buccal and lingual surfaces, almost covering several teeth, and presenting raw ulcerations in the area of the left upper third molar. (Fig. 1.) The submaxillary lymph nodes bilaterally were moderately enlarged, firm and tender, but no other lymphadenopathy was evident. Aside from the seven months' gravid uterus the remainder of the physical examination was not remarkable. There was no enlargement of the liver or spleen by palpation or by percussion.

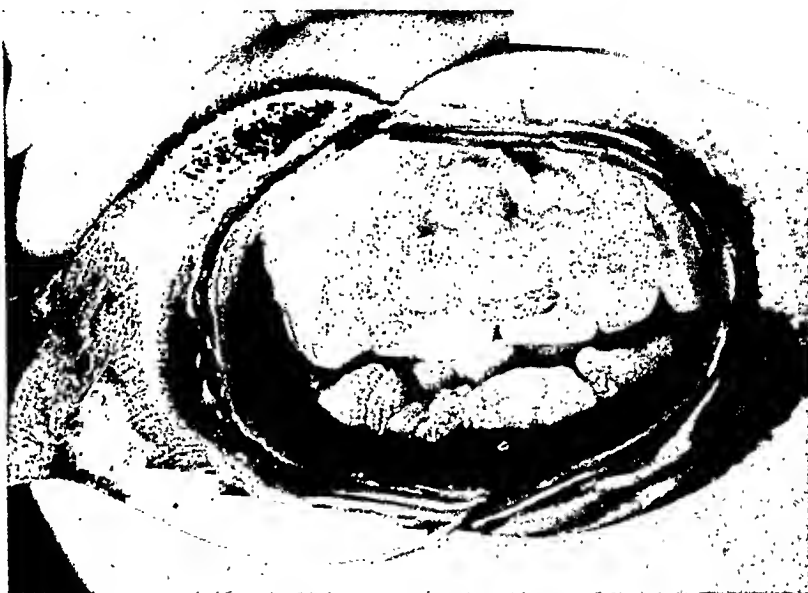


Fig. 1.—Showing the marked generalized hypertrophy of the gums.

Among the admission laboratory data was included a urinalysis which was negative except for a trace of albumin. The hemoglobin was 61.6 per cent (9.5 Gm.—Haden), red blood cells 2.1 million, and the white blood cells nine thousand, two hundred.

Course.—The patient was studied by the dental service and started on a high protein diet, daily intravenous administrations of 500 mg. of ascorbic acid and soluble B-complex vitamins, mouth irrigations with hydrogen peroxide, and parenteral penicillin therapy (120,000 units per day).

Her mouth continued to be painful but the oral hygiene improved and the submaxillary lymphadenopathy became less marked and tenderness over the glands decreased. A low-grade diurnal fever became persistent. Roentgenogram of the chest showed no evidence of disease of the lung.

Transfusions of whole blood were given on the tenth and fifteenth hospital days, and on May 17 the hemoglobin concentration had risen to 71.4 per cent of normal (11.0 Gm.), and the red blood cells to 4.0 million. The several total leucocyte counts done during these first weeks in the hospital were considered to be within the range of normal (9,200; 10,500; 8,250).

The patient was transferred to the Obstetrical Division on May 22, at which time the physical findings were essentially similar to those noted on

admission. The following day a complete blood count revealed hemoglobin 71.4 per cent (11.0 Gm.), red blood cells 4.0 million, white blood cells 21,000 with neutrophils 7 per cent, lymphocytes 27 per cent, and 66 per cent blast forms (later identified by Dr. L. M. Toeantins as monoblasts). The platelet count was 310,000 per cubic millimeter, hematocrit 33 per cent, and the erythrocyte sedimentation rate was 41 mm. per hour (Wintrobe method). The bleeding time was 3 minutes, and the coagulation time was 4½ minutes. The tourniquet test and heterophile antibody test were negative.

The program of oral hygiene, ascorbic acid, and prophylactic penicillin therapies, and transfusions as indicated was continued. On May 29 a gingival biopsy was done. The section is illustrated in Fig. 2.



Fig. 2.—Biopsy of gingival tissue. The submucous stroma is densely infiltrated with mononuclear cells, separating the compact fibrous tissue bundles. ($\times 130$.)

By June 6, despite a blood transfusion of 500 c.c., the hemoglobin had fallen to 58.4 per cent (9.0 Gm.); and the white blood count was 35,600, with 2 per cent neutrophils, 38 per cent lymphocytes, and 60 per cent monoblasts.

Cesarean section, first scheduled for June 12, was done on June 8, two hours after spontaneous rupture of the membranes. Under continuous spinal anesthesia the patient was delivered of a living normal male infant weighing 5 pounds 12 ounces. The baby was normal in all respects, with normal hematologic findings, and was discharged from the hospital 7 ounces over the birth weight on the twentieth day of life.

At operation, aside from a moderate amount of ooze from all cut vessels, hemostasis was not troublesome, and the patient seemed to withstand the procedure very well.

Although the gingival hypertrophy became less pronounced, from the time of operation until her death twelve days later her course was rapidly downhill, in spite of penicillin therapy (later sulfadiazine) and transfusions of whole blood. Abdominal distention, dyspnea, pallor, and weakness became profound, and her temperature showed progressive elevation and irregularity. On June 15 the liver and the spleen were palpably enlarged, and the patient complained of pains in the left upper quadrant of the abdomen. On this date the hemoglobin was 68.1 per cent (10.5 Gm.), white blood cells 65,000, with a differential count essentially as before. The platelet count was 100,000, the bleeding time 30 seconds, the hematocrit 30 per cent, and the sedimentation rate was 54 millimeters per hour.

On June 18, marked air hunger supervened and petechial hemorrhages were noted. Despite transfusion and oxygen therapy, she expired on June 20.

Complete postmortem examination was performed seven and one-half hours after death by Dr. D. N. Twaddell.

Postmortem Examination.—Pathological diagnosis, acute monocytic leukemia, with leucemic infiltration of all organs, monoblastemia, petechial hemorrhages of all organs, acute ulcerative gingivitis, multiple infarcts of the spleen, pulmonary edema, and postpartum involution of the uterus.

External Examination.—Numerous petechial hemorrhages were seen over the entire body. The skin was of a dusky hue but was not jaundiced. There was a healing operative incision in the lower mid-abdomen. A few soft submaxillary nodes were barely palpable, but elsewhere the superficial nodes could not be felt. A blood tinged froth was present in the oral and the nasal passages. The gums were markedly swollen and hemorrhagic, with extension of the margins progressively along the teeth. This hypertrophy of the gums appeared about the upper and the lower teeth and on both buccal and lingual surfaces. On the roof of the mouth the mucous membrane was involved as far as the soft palate. The breasts were of firm consistency throughout. The abdomen was slightly distended, and in the suprapubic region there was a fullness occasioned by the enlarged involuting uterus. There was no peripheral edema.

Internal Examination.—There were petechial hemorrhages over both parietal and visceral peritoneal and pleural surfaces. The peritoneum in the region of the operative site was completely healed.

Bone marrow: The bone marrow of the ribs and vertebral column was remarkably pale but otherwise not grossly abnormal.

Lungs: The lungs were unusually firm throughout, and on cut section both upper lobes and the right middle lobe (and, to a lesser extent, the lower lobes) exhibited a considerable amount of diffuse infiltration and areas suggestive of consolidation.

Heart: Except for scattered subepicardial hemorrhages the heart was grossly normal.

Spleen: The spleen was enlarged to 4 cm. below the costal margin, weighed 1,010 Gm., and presented a tense congested capsule with many diffuse hemorrhages; on cut section marked congestion and scattered hemorrhages were seen; Malpighian bodies and trabeculae were not discernible.

Gastrointestinal tract: The stomach was moderately distended with gas and showed many submucosal hemorrhages but no ulcerations. The small intestine was collapsed and contained a considerable quantity of dark coagulated

blood, particularly in its distal segments; throughout its length Peyer's patches were markedly enlarged, especially in the region of the ileocecal valve where several patches measured 1.5 cm. in diameter and were elevated 4 mm. above the remainder of the surface of the mucous membrane. The ileocecal valve itself was the site of ulceration with accumulation of a fibrinous, diphtheritic, markedly hemorrhagic exudate, but there was no obstruction. The mesenteric lymph nodes were firm but only slightly enlarged.

Liver: The markedly enlarged liver weighed 2,600 Gm. and was of a very soft consistency; there were no hemorrhages but a leucemic infiltration throughout all the portal areas was obvious.

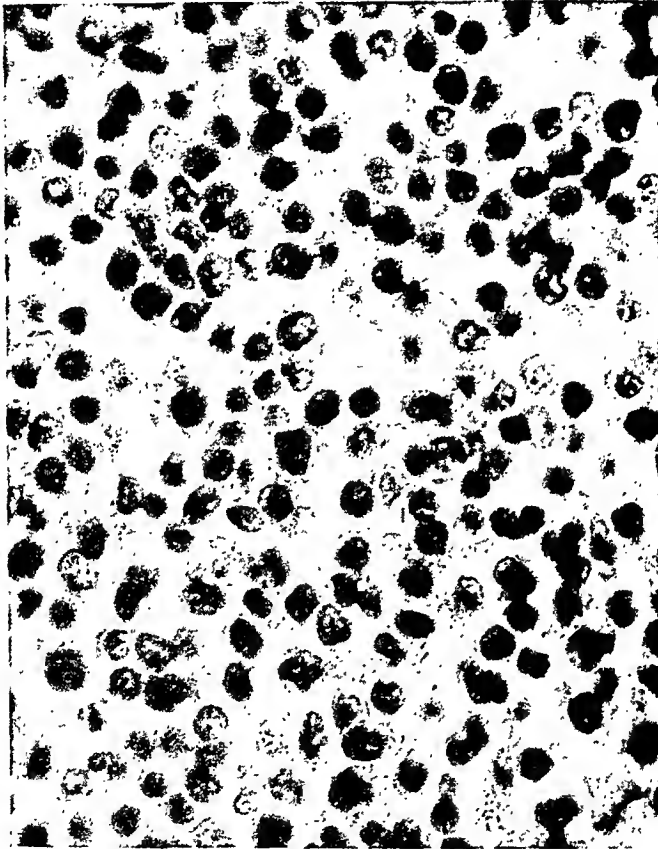


Fig. 3.—Photomicrograph of a section of one of the uterine blood vessels, showing the typical cell found in the blood and in the widespread infiltrations. Oil immersion. ($\times 1225$.)

Kidneys: The kidneys, large and swollen, exhibited cortical petechiae and widespread leucemic infiltration of both cortical and medullary tissue.

Pelvic organs: Both ovaries were large and firm. The uterus was symmetrically enlarged and the operative incision in its substance was well healed.

Brain: Examination of the brain revealed no gross abnormalities save for two small areas of recent hemorrhage in the dentate nucleus of the left cerebellar hemisphere.

Microscopic Examination.—The striking feature of the microscopic examination was the widespread and diffuse infiltration of all organs and tissues studied—breast, thymus, heart, lungs (Fig. 4), diaphragm (Fig. 5), spleen (Fig. 6), peritoneum, intestines, mesentery, pancreas, liver, gall bladder, adrenals, kidney (Fig. 7), pelvic organs, lymph nodes, thyroid, bone marrow,

gingivae, tongue, and brain. The typical cell was nonpleomorphic and averaged 15 micra in diameter with a single oval to reniform vesicular nucleus and a large amount of eosinophilic cytoplasm (Fig. 3).

Heart: There was a generalized infiltration of the epicardium with the neoplastic cells which appeared in small clusters throughout the fatty tissues, the interfibrillary tissue of the myocardium, and the endocardium.



Fig. 4.—Photomicrograph of a section of the lung showing invasion of alveoli and interstitial tissue with monoblasts. ($\times 200$.)

Lungs: Similar pathologic changes were seen in the lungs with collections of mononuclear cells in the subpleural areas, within blood vessels and small bronchi, and along the septa and alveolar walls; there was considerable hemorrhage throughout the lung parenchyma with small areas of necrosis, and alveoli containing edema fluid, erythrocytes and monoblasts.

Pelvic structures: Of the pelvic structures the ovarian stroma, Fallopian tubes, serosa, myometrium, venous sinusoids, and necrotic decidual tissues were heavily invaded by islands of leucemic cells, and there were monoblasts engulfed in the meshes of fibrin of the intrauterine clot. Unfortunately, the placenta was inadvertently discarded.

Lymph nodes and bone marrow: The architecture of both medullary tissue and lymphoid follicles of the lymph nodes and the spleen was markedly distorted and in the vertebral and costal bone marrow the fat was entirely absent, the space being occupied by densely packed mononuclear elements with only occasional myeloid and erythroid cells apparent.



Fig. 5.—Photomicrograph of a section of diaphragm, with infiltration of the interfibrillary tissue. (×200.)

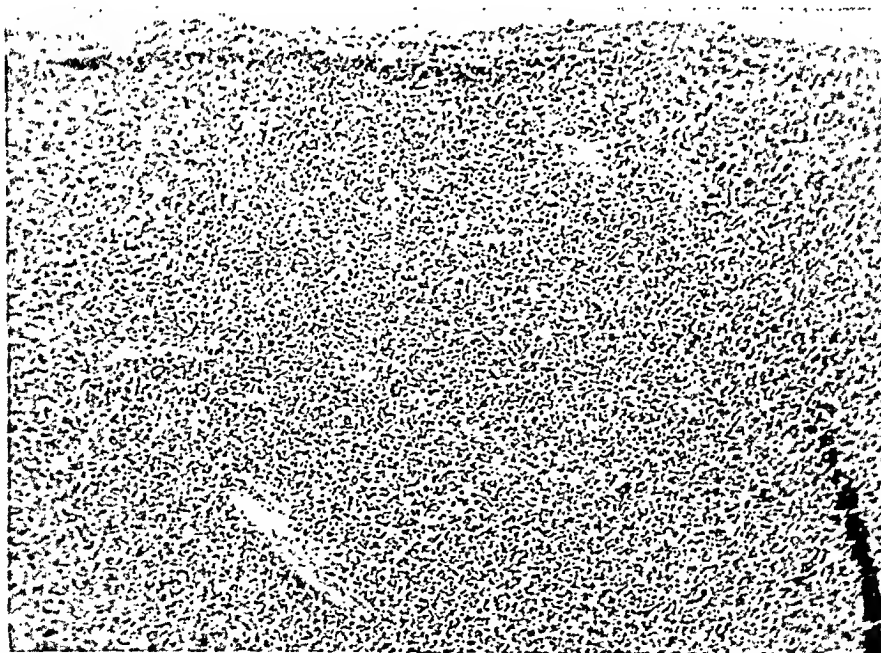


Fig. 6.—Photomicrograph of a section from the spleen. Distortion of the normal architecture is clearly seen. (×130.)

Gingivae: The gingivae, by biopsy and by necropsy, exhibited dense infiltration of the submucous stroma with mononuclear cells, and areas of ulceration but no polymorphonuclear leucocytes were seen. (Fig. 2.)

Brain: Even the brain was not spared, with scattering of monoblasts in the perivascular tissue, cerebrum, cerebellum, and the pituitary gland.

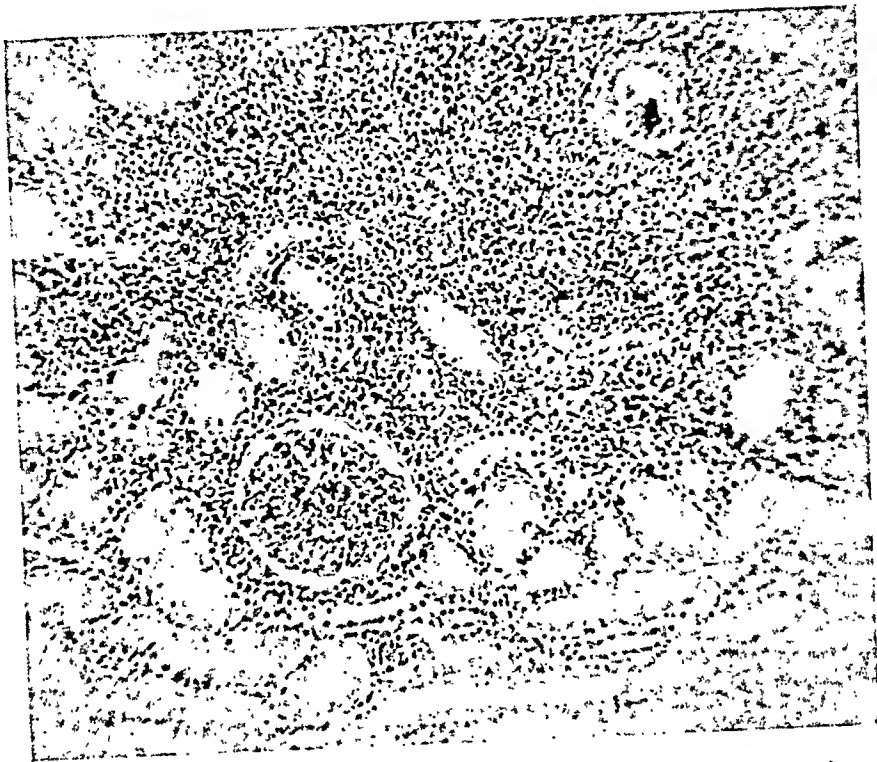


Fig. 7.—Photomicrograph of a section of kidney, showing the heavy invasion of stroma and glomeruli. ($\times 200$.)

Comment

In the first patient it seems probable that the leueemic state antedated conception and gestation by at least several months; while in the second instance onset during pregnancy seems likely. The course and the findings at autopsy in the patient with acute monocytic leueemia, though unique in obstetric literature, are in close accord with previous reports of this disease,^{2, 3} the natural history of which was apparently not altered by the complicating pregnancy.

Similarly, there are numerous discussions in the literature of the significance of oral lesions in leueemia.²⁻¹¹ While gingival hypertrophy and ulceration do occur occasionally in other types of leueemia,^{5, 10, 12} and the oral manifestations of all types of acute leueemia are said to be similar,⁷ these changes have been observed in 52 per cent.⁵ to 80 per cent.¹¹ of cases of acute monocytic leueemia and are considered by some to be so characteristic that the diagnosis should be suspected on clinical grounds alone.^{9, 11, 13} It is also noteworthy, though familiar, that pathologic changes in the gums may be the first manifestations of the disease, as in Case 2.

The medical management of both of these cases was of a supportive nature. Although it has been suggested that Fowler's solution or even irradiation could be administered with relative impunity during gestation,¹⁴⁻¹⁸ it was felt that the

TABLE I. TABULATION OF CASES REPORTED SINCE THE LAST REVIEW OF THE LITERATURE¹

CASE NO.	AUTHOR	YEAR	AGE	PARA	RELATION OF ONSET TO GESTATION	PERIOD		HEMORRHAGE	RESULTS		TYPE OF LEUCENIA
						GESTATION WHEN	DELIVERY HOW		MOTHER	CHILD	
1	Holmgren ²⁰	1944	40	v	1½ yr. prior	Term	Spont.	None	Lived	Lived	Chronic myelogenous
2	Hochman ¹⁶	1944	25	i	22 mo. prior	2 mo.	Induced abortion	None	Died 4 mo. postop.	Nonviable	Chronic myelogenous
3	Hochman ¹⁶	1944	23	i	1½ yr. prior	Term	Spont.	None	Died 10 mo. post partum	Lived	Chronic myelogenous
4	Applebaum ¹⁹	1944	29	0	3 mo.	7½ mo.	C. sect.	—	Died several hours post partum	Stillborn	Acute myelogenous
5	Angelucci ¹⁷	1944	22	0?	4 mo. ?	Term	Forceps	None	Lived	Lived	Chronic myelogenous
6	Miles and Wheeler ¹⁸	1945	30	viii	6 mo. prior?	Term	Spont.	None	Lived	Lived	Chronic myelogenous
7	Miles and Wheeler ¹⁸	1945	30	ii	Prior	8 mo.	Spont.	Yes	Lived	Lived	Chronic myelogenous
8	Bright and Hayes ²¹	1946	23	i	4-5 mo.	Term	Spont.	None	Died 3 mo. post partum	Lived	Acute lymphatic

absence of symptoms in the first patient interdicted such treatment. There is no known therapy that alters the course of acute leucemia; irradiation is apparently seldom of even temporary aid and may cause severe reactions^{2, 4}; blood transfusions may be of transient value.

The indication for cesarean section in the second patient was a previous section, while in the patient with chronic leucemia it was the maternal disease which indicated this method of delivery. The validity of leucemia as an indication for a section is not upheld by previous observations in the literature. Moloney et al.¹⁵ reported a woman with chronic myelogenous leucemia successfully delivered by section (the indication being uncontrollable toxemia) without apparent ill-effect on mother or child. This same author was able to find reports of three other leucemic women delivered by this method; two of the infants thus obtained were stillborn, and all of the mothers died within eleven days after delivery. Appelbaum¹⁸ describes a case of acute myelogenous leucemia with cesarean delivery at seven and one-half months; the infant was stillborn, and the mother died several hours post partum. All of which tends to corroborate the statement of Grier and Richter¹⁴ that interference with pregnancy does not help the mother in either acute or chronic leucemia, that it only tends to produce premature and nonviable babies, and that in the acute form it shortens the mother's life.

A rapid downhill course following delivery has been previously reported.¹ Although this was true for the second patient, it would be unwise to draw any conclusions in view of the precipitous course of monocytic leucemia.

Premature labor has been seen in the majority of cases, but severe hemorrhage, post partum or during delivery by any method, has been uncommon—9 instances of 88 with 3 deaths.

With critical review of the literature, it is safe to conclude that pregnancy has little, if any, effect on the course of leucemia. Conversely, however, McGoldrick¹ found maternal mortality 100 per cent and fetal mortality 60 per cent for the acute forms, while the mortality was 36.5 per cent and 16.4 per cent, respectively, for the chronic types. It is interesting that a leucemic mother has never been reported as producing a leucemic child.

The eight cases that have accumulated since McGoldrick and Lapp wrote their paper do not warrant statistical re-evaluation of the problem. Following the scheme of Grier and Richter, these reports are presented in Table I.

Summary

1. The literature has been reviewed and two cases added, bringing the total number of reported cases of pregnancy associated with leucemia to ninety.
2. A case of chronic myelogenous leucemia complicated by pregnancy, with the mother still living more than a year after delivery, is presented.
3. A fatal case of acute monocytic leucemia complicating pregnancy, with a discussion of necropsy findings, is presented. No similar case has been found in the literature.
4. Leucemia per se does not require any special obstetric management.

5. On the basis of reported cases leukemia is not transferred from mother to child.

6. Although in the two cases here reported no unusual bleeding was encountered, it must be recalled that of the eighty-eight previously reported cases serious hemorrhage occurred in nine, with three deaths attributable to this cause.

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THE EFFECT OF EQUINE GONADOTROPIN (GONADOGEN) ON THE HUMAN OVARY

SAMUEL A. WOLFE, M.D., F.A.C.S., AND IRWIN NEIGUS, M.S., M.D.
BROOKLYN, N. Y.

(From the Department of Gynecology, Brooklyn Jewish Hospital)

THE gonadotropic activity of equine gonadotropin and the experimental production of ovulation by this agent in the human being have been the subject of much investigation in the past decade. The findings, however, have been varied and contradictory. The research of Aschheim and Zondek¹ and Smith and Engle² in this country has shown that ovarian function is regulated by the anterior lobe of the pituitary. The demonstration of the gonadotropic activity of pregnancy urine and of extracts of the anterior lobe of the pituitary gland soon led to the experimental production of ovulation in laboratory animals. This gave impetus for similar investigations in the human female.

Using chorionic gonadotropin, Campbell,³ Geist,⁴ Hamblen,⁵ Geist, Gaines, and Salmon,⁶ and others were unable to demonstrate the production of growth and maturation of the Graafian follicle and ovulation in women. Hamblen⁷ and other investigators also failed to demonstrate ovulation in women, following the administration of anterior pituitary extract.

A new source of gonad-stimulating hormone was discovered in 1930 by Cole and Hart⁸ in the blood of pregnant mares. It resembled extracts of the anterior pituitary gland in its physiologic properties, by producing follicular development, ovulation, and corpus luteum formation in hypophysectomized animals. Gross and Cole,⁹ Catchpole and Lyons,¹⁰ and Hamburger¹¹ were successful in producing fertile ovulation in rats, ewes, sows, and cows by the injection of pregnant-mare serum. In 1938, Davis and Koff¹² reported that they produced ovulation in women by the intravenous use of pregnant-mare serum in half of their cases. This work was confirmed by Siegler and Fein,¹³ who reported artificial ovulation in 16 of 30 women. Hartman,¹⁴ working with adult monkeys, found a reasonable certainty of stimulated ovulation in only 7 of 104 cases. Watson, Smith, and Kurzrock¹⁵ reported that they were able to stimulate follicular development in women with the hormone of pregnant-mare serum, but could not show ovulation in any of their cases. Geist, Gaines, and Salmon¹⁶ reported the results of equine gonadotropin administered intravenously or intramuscularly in 22 women. In no instance was conclusive evidence of artificially induced ovulation found. Brewer, Jones, and Skiles¹⁷ also administered equine gonadotropin intramuscularly to 24 women subjected to laparotomy, and reported failure to induce ovulation. Greenblatt¹⁸ reported stimulation of the various components of the ovary following gonadotropin administration, but orderly maturation did not occur.

As studied by endometrial biopsy, Griffith and McBride¹⁹ reported induced ovulation with equine gonadotropin in 7 of 8 patients with anovulatory cycles. On the other hand, Erving, Sears, and Rock²⁰ reported no evidence of stimulation in the ovaries in 16 anovulatory patients as determined by endometrial biopsies.

TABLE I. EFFECT OF GONADOGEN UPON OVULATION

CASE	AGE	MENSTRUAL INTERVAL	INJECTION DAY OF CYCLE	NO. OF UNITS	OPERATION DAY OF CYCLE	PROOPERATIVE ENDOMETRIAL B'OPSY	CURRENT C. L.	INDUCED OVULATION
1	42	30	23	60	24	Atrophic, interval fibroid	+ Effl.	0
2	25	28	16	60	17	Interval	+ Cong.	0
3	31	12-20	7	60	9	Postmenstrual	+ 0	0
4	44	26-28	21	60	22	0	0	0
5	34	14-21	17	60	22	0	+ Invol.	0
6	48	28	23	60	25	Initial premenst.	+ Late vasc. (double)	0
7	45	28	19	60	25	0	+ Cong.	0
8	40	26-28	14, 15	60, 60	20	0	+ Late vasc.	0
9	38	28	23	60	25	Mixed premenst.	+ Effl.	0
10	44	Irreg.	22	60	23	Premenstrual	+ Effl. (double)	0
11	49	Irreg.	8	60	10	Postmenstrual	+ 0	0
12	38	28	26	60	28	Premenstrual	+ Effl. (double)	0
13	40	28	22	60	23	0	+ Effl. (double)	0
14	47	Irreg.	?	60	27 hours after inj.	Prolif., late	+ Cong. (double)	0
15	45	26-28	7	60	9	Prolif.	0	0
16	45	30	9	60	15	Postmenstrual	+ Cong.	0
17	34	28	6	60	9	0	0	0
18	37	28	7	60	9	0	0	0
19	35	14-42	14	60	19	Prolif., late	+ Early vasc.	0
20	33	Amen.	—	60	24 hours after inj.	Uterus absent	+ Vasc. (double)	0
21	42	27	10, 12	60, 30	14	Early prolif.	0	0
22	36	14-28	12	60	13	Prolif., late	+ Early vasc.	0

It is evident that the present status of equine gonadotropin is far from clear. Hamblen²¹ states, "Equine gonadotropin has the ability to stimulate follicular activity in the human being and in the monkey, but ovulation and corpus luteum formation are not induced." On this basis, for the treatment of anovulatory failure, he has supplemented equine gonadotropin for its follicle-stimulating properties by chorionic gonadotropin for its luteinizing ability.

Material

Because of many conflicting reports obtained, we felt it wise to review by a new study the actual effects on the human ovary by equine gonadotropin. Twenty-two women were selected for this study. All patients utilized in this investigation, with one exception, were subjected to laparotomy because of a fibromyoma uteri. Case 20 had had a previous hysterectomy and left salpingo-oophorectomy. Laparotomy was performed for a parovarian cyst. The right ovary was originally left in situ.

The ages of the women varied from 25 years to 49 years. One patient was 25 years of age. There were 5 patients in the 31 to 35 age group, 5 patients in the 36 to 40 age group, 8 patients in the 41 to 45 age group, and 3 patients in the 46 to 49 age group.

The menstrual periods had been regular except in 7 patients, who had recent menometrorrhagia. One patient (Case 20) had had long-standing amenorrhea after hysterectomy.

Prior to laparotomy, a vaginal smear and endometrial biopsy were performed. Vaginal smears were not contributory. After preliminary skin and ophthalmic sensitization tests, the equine gonadotropin was administered intravenously in varying dosage and for a variable period of time prior to operation. The average dose was 60 Cartland-Nelson units of Gonadogen. In 2 cases, 90 units were administered, and in one case each, 100 and 120 units of Gonadogen. The interval between administration of the Gonadogen and operation varied from 24 hours to 146 hours with an average of 60 hours. The administration of the drug and laparotomy were performed at different times during the menstrual cycle. The drug was administered in the first half of the menstrual cycle in 5 cases, in mid-cycle in 4 cases, in the second half of the cycle in 12 cases. At operation, the uterus, both ovaries, and tubes were removed whenever feasible, and sections were taken from the uterus, to study any changes in the endometrium, and from all cystic areas in all ovaries. The findings are summarized in Tables I and II. Basically, as will be seen from the records, ovulation was not observed.

We can now proceed with a summary of changes induced in the human ovary as observed after Gonadogen:

Stromal Changes.—Universal edema of the ovaries was not observed, either on gross or microscopic examination, but occasionally was pronounced in the theca externa about follicular cysts. Hyperemia, however, was common and the entire organ often assumed a pink-gray appearance. This was especially noted in 12 of the cases. Perifollicular and intrafollicular hemorrhage was a striking finding and occurred in 16 cases of the group (Fig. 1). The numerous, tense, red or red-blue cysts studding the cortex were a dominant finding after Gonadogen stimulation. Pseudodecidual changes of the stromal cells were noted in Case 1. Clusters of fusiform and round stromal cells with pink or blue-pink cytoplasm and a central vesicular nucleus were noted in the cortex just beneath the tunica. They resembled similar collections seen in the normal ovary at the end of pregnancy.

Vascular Apparatus.—In practically all cases, engorgement of capillaries was marked. It reached its zenith in the vessels of the theca externa of the

TABLE II. EFFECT OF GONADOGEN ON FOLLICULAR APPARATUS OF HUMAN OVARY

CASE	FOLLICULAR HEMORRHAGE				PSEUDOLUTEINIZATION OF GRANULOSA CYSTS OR CURRENT MATURING FOLLICLE	THECA INTERNA CYSTS	THECA INTERNA HYPERTROPHY	TRUE LUTEINIZATION OF UNRUPTURED FOLLICLE	UTERINE ENDOMETRIUM
	PERI- FOLLICULAR	INTRA- FOLLICULAR	INTER- STITIAL						
1			+	+			+	+	Interval Late interval Prolif.
2									
3	+	+			Old—f				
4			+	+	Old—f	+			Interval Premenst.
5	+				Recent	+			Late interval Initial premenst.
6	+					0		0	
7	0			0		+			
8				+			+		
9					Old	+			Late premenst. Premenst.
10	+	+		+		+			Early interval Premenst.
11					Current marked	+			Late premenst. Late interval Interval
12						+			Interval Interval
13							+		Interval Late interval
14			+	+					Interval Interval
15	+	+		+	Current—marked				Interval Interval
16	+	+					+		Interval Interval
17	+	+			Old and recent				Interval Interval
18	+	+		+	Old				Interval Late interval
19	+	+		+	Recent				Interval Late interval
20						+	+	+	Interval Interval
21	+				Recent		+	+	Early prolif. Late interval
22	+	+			Recent		+	+	Late interval

more recent follicular cysts. Diapedesis resulted in free red cells in the edema fluid about the cysts (Fig. 2). Actual rupture with resulting interstitial hemorrhage was frequent, the escaping blood breaking through the overlying columns of the theca and granulosa cells to reach the cavity of the cyst. We do not feel that convolution of the pseudoluteinized follicle is due to pressure by the engorged thecal vessels upon the overlying theca and granulosa layers. Reference to resultant interstitial perifollicular and intrafollicular bleeding has been made above.



Fig. 1.—Ovaries after Gonadogen. Perifollicular and interstitial bleeding is prominent.

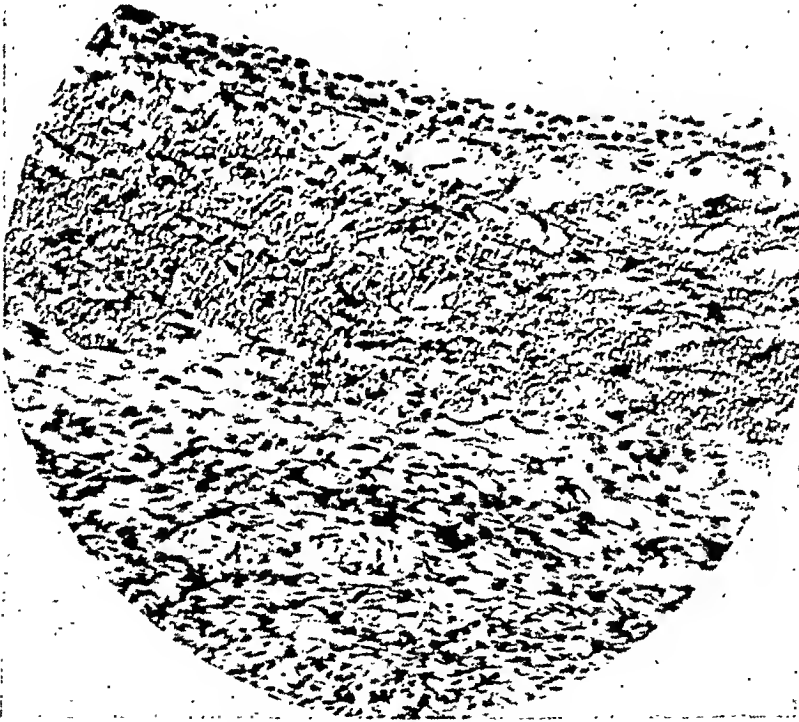


Fig. 2.—Case 6, right ovary. Old follicular cyst with perifollicular bleeding and edema.

Follicular Apparatus.—In this study we have been unable to find evidence of Gonadogen stimulation of the follicle, either by (a) multiplication in the number of maturing follicles or (b) the acceleration in tempo of the ripening

of an individual follicle. In 5 cases (Nos. 2, 13, 14, 15, and 20) maturing follicles with discus proligerus were observed. The ovum was seen in 3 cases (Nos. 2, 14, and 15). In Cases 2 and 14, the ova were disintegrating. The follicles were in association with a corpus luteum of congestion and, therefore, attributable to the current cycle. The time of Gonadogen injection and the menstrual dates further support this view. In Case 13, the maturing follicle with a discus was associated with double corpus of efflorescence in the same ovary but no ovum was seen in two or three sections studied. In Case 20, a maturing follicle with an ovum in the discus was found in the right ovary, which was also the seat of a double corpus of vascularization. Whether this was an early atresic follicle which began maturation concurrently with the two others transformed into corpora cannot be told. The gap in the knowledge of the time required for disintegration of an ovum and its discus in an unruptured follicle allows no answer. In all these cases, the granulosa layer of the maturing follicles showed an increment of cell cytoplasm and the theca interna was especially prominent. Theca changes were especially marked in Cases 2 and 20.

"Pseudoluteinization of follicle cysts," so designated by Greenblatt, was observed in Cases 11 and 15 (Figs. 3 and 4). These are currently-maturing follicles and are often mistaken for newly ruptured follicles in the incipient stage of lutein transformation. Indeed, this finding may have been the pitfall for those investigators who ascribed follicle maturation and rupture to equine gonadotropin. Both have compressed cavities with an irregular margin, but in the normally ruptured follicle a stigma or "punktum" is grossly present. The cavity is truly collapsed and the lining shows marked dentation. The normal early lutein cell is granular with pink acidophilic cytoplasm. The nucleus is round and deeply staining. The cell body soon elongates (Fig. 5). Clear lutein cells are not seen in a normal corpus until vascularization is reached, but at this time the corpus is grossly seen beneath the tunica, even when not dendritic. On section, the wide central cavity and its bloody coagulum contrast with the convoluted gray-yellow lutein lining. The clarity of the cell in the "pseudoluteinized follicle" is the initial episode and begins in the cell cytoplasm prior to rupture of the follicle. It is attributable to the excess lipid deposit resulting from perifollicular engorgement. The irregular hypertrophy of the cells due to lipid deposition may well be the cause of the irregular configuration of the central cavity. In sections after scharlach R stain, we have seen similar lipid deposits in the granulosa cells of follicle cysts. Intracellular edema is excluded by the uniform staining and lack of nuclear and membranous changes of the cell body. It is worthy of note that those instances of "pseudoluteinization" were in ovaries injected on the seventh and eighth day of the cycle and that a corpus luteum of the current cycle was not observed. Whether an artificially lipidized follicle can proceed to maturation, rupture, and liberation of a normal ovum cannot be told.

True luteinization in an unruptured follicle was noted only once (Case 1, Fig. 6). In the same patient, clusters of decidua-like cells were noted in the ovarian cortex. A corpus luteum of efflorescence of the current cycle was present in the (other) right ovary. Grossly, the luteinized follicle presented as a minute hemorrhagic cyst on the surface of the left ovary. Microscopically, the cavity was round and spherical and contained free blood. Though not universally present, the cavity presented two to seven layers of true lutein cells. The cells were large, ovoid or round, with clear cytoplasm, and a central nucleus. The theca externa, composed of eight or nine layers of smaller cells, was well differentiated. Huge capillary sinusoids coursed concentrically between granulosa and theca interna. The small round cavity contrasted with the large lining lutein cells. Certainly, rupture of the follicle and normal corpus luteum forma-

EFFECT OF GONADOTROPIN ON OVARY

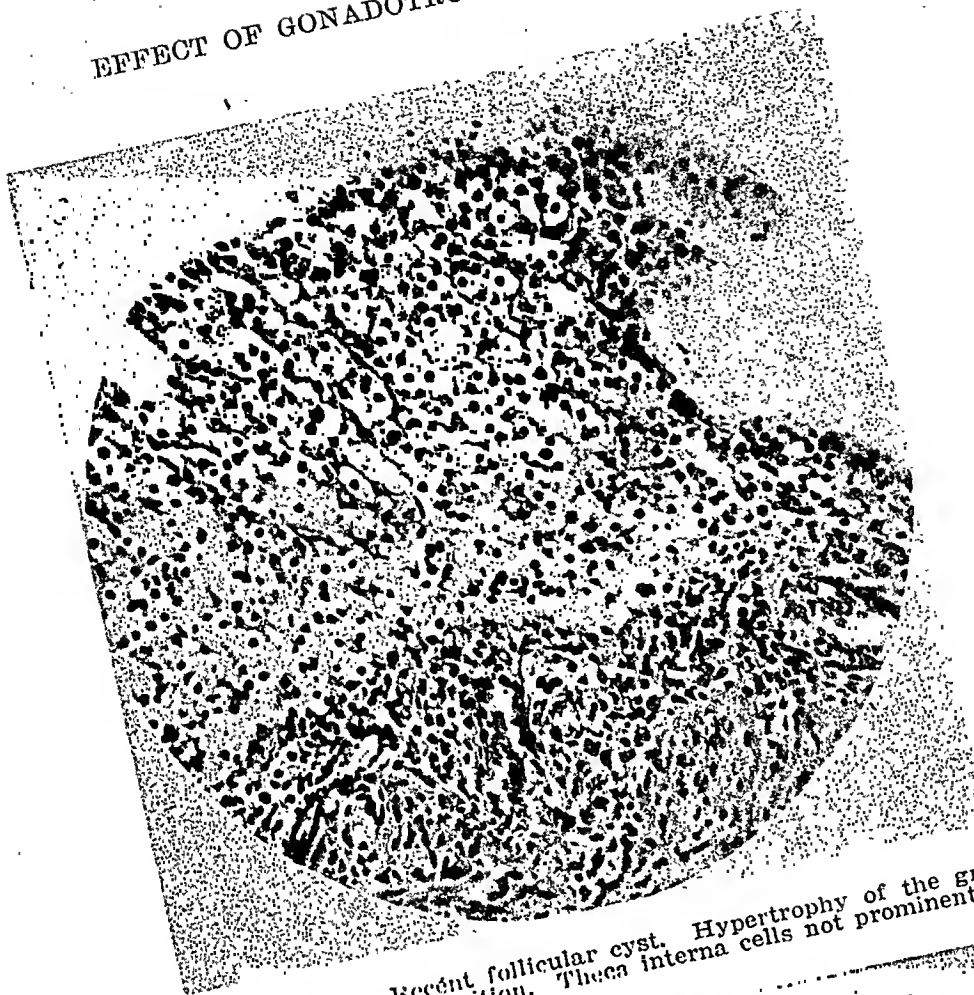


Fig. 3.—Case 5, right ovary. Recent follicular cyst. Hypertrophy of the granulosa cells due to early lipid deposition. Theca interna cells not prominent.

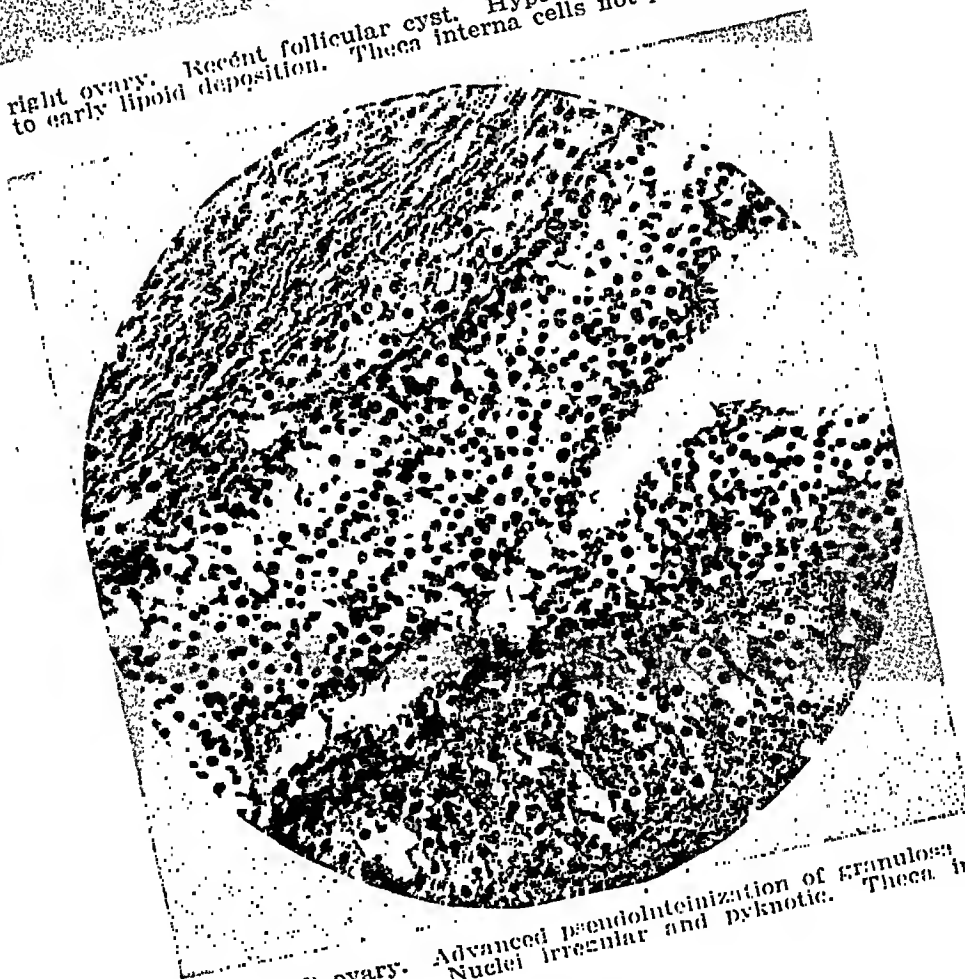


Fig. 4.—Case 11, left ovary. Advanced pseudointerminization of granulosa cells in a maturing follicle of the current cycle. Nuclei irregular and pyknotic. Theca interna cells more prominent and surround the vessels.

tion cannot be substantiated. This change is unusual and has not been noted by other investigators. It resembles luteinized unruptured follicles of the rabbit ovary stimulated by chorionic gonadotropin.

Follicular Cysts.—Except in old follicle cysts with atrophic cells, the granulosa-cell column and the underlying theca showed decided morphologic changes. Grossly, the cysts were larger and more prominent than normal, often

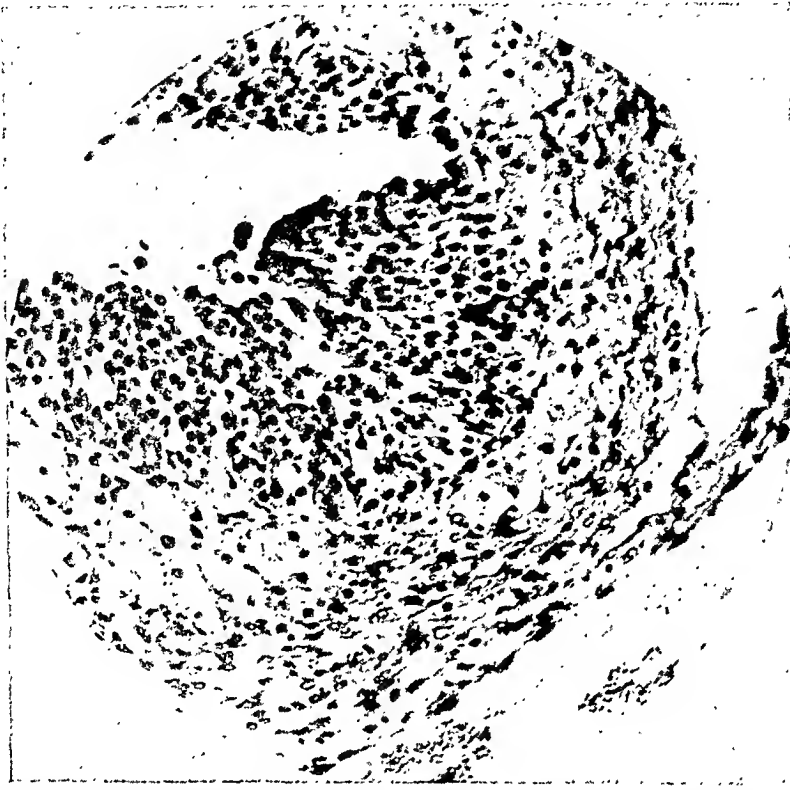


Fig. 5.—Case 14, right ovary. An early corpus luteum of congestion. Note that the lutein cells are not clear and ovoid as above. They are elongated, small, granular and deeply staining.

reaching to 15 to 20 mm. in diameter, with a range from 2 to 25 mm. (Fig. 7). The grossly hemorrhagic appearance has been previously noted. True blood in the cavity was found in four instances. An increased number of follicular cysts could not be established, for there are no criteria even in normal ovaries. Microscopically, the number of cell layers in the granulosa column was seemingly dependent upon the age of the cystic follicle. Yet strikingly irrespective of age, all granulosa cells were larger than normal with a definable amount of pink-staining cytoplasm (Fig. 8). No distinct nuclear changes were apparent, although staining intensity was often slightly increased. As already described, in the most recent follicles, the round central cavity was replaced by a compressed dentate type lined by a serpiginous epithelial column of granulosa cells. Lipoid deposition in the cell body caused marked enlargement of the cell and clarity of its cytoplasm, thus simulating the lutein type. Such follicle cysts are designated as the "pseudoluteinized" type and were encountered in Cases 11 and 15. (See Figs. 3 and 4.) All such follicles were in ovaries injected between the ninth and sixteenth day of the cycle and lipoidization and enlargement of the cells is interpreted as a Gonadogen effect on the granulosa cells of a maturing but unruptured follicle.

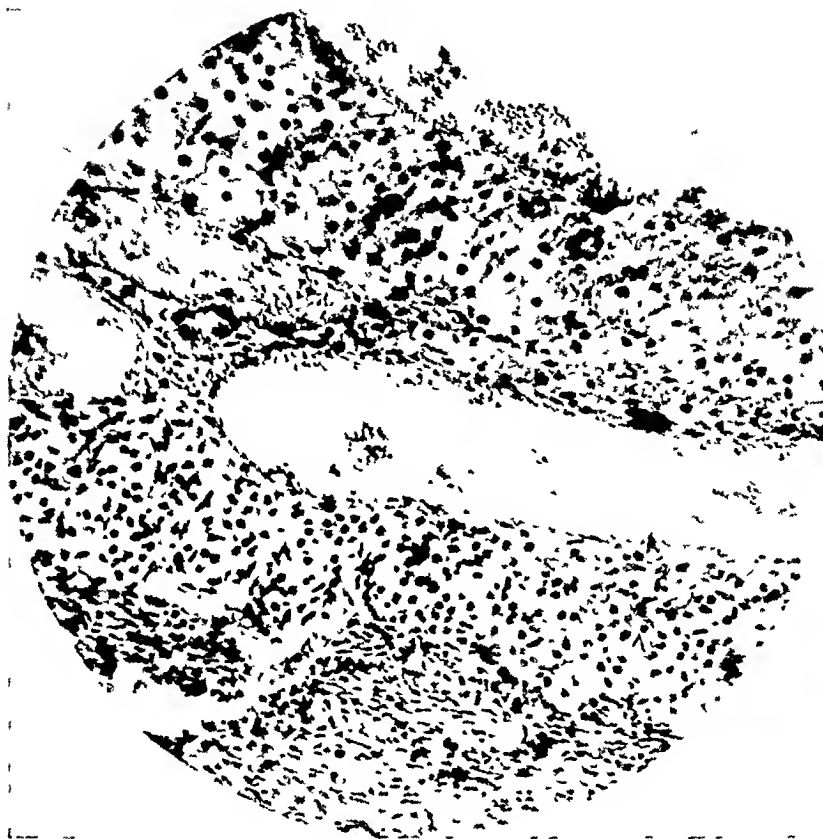


Fig. 6.—Case 1, left ovary. True luteinization of an unruptured follicle. Huge sinusoids underlie the lutein column followed by the broad theca interna zone. The latter cells are smaller and clearer.

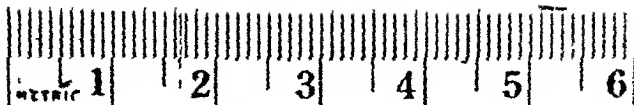


Fig. 7.—Case 20, right ovary. Note the double corpus luteum of the same developmental age. The follicular cysts at the periphery are large and prominent. The central one shows marked perifollicular hemorrhage.

Theca Interna.—Changes induced by Gonadogen were most prominent in the theca interna cells. Follicles in every development and regressive stage showed such effects. Even in corpora fibrosa, clusters, islands, or palisaded columns of theca cells were demarcated and surrounded by cellular stroma (Fig. 9). Occasional too solid islands of hypertrophied theca cells were observed, as often seen in an ovary at the end of a normal pregnancy. The large clear cell, its sharp outline, and its central nucleus were prominent. In fairly recent follicles, theca-cell hypertrophy was so pronounced that at times only the presence of the overlying granulosa permitted true recognition (Fig. 10).

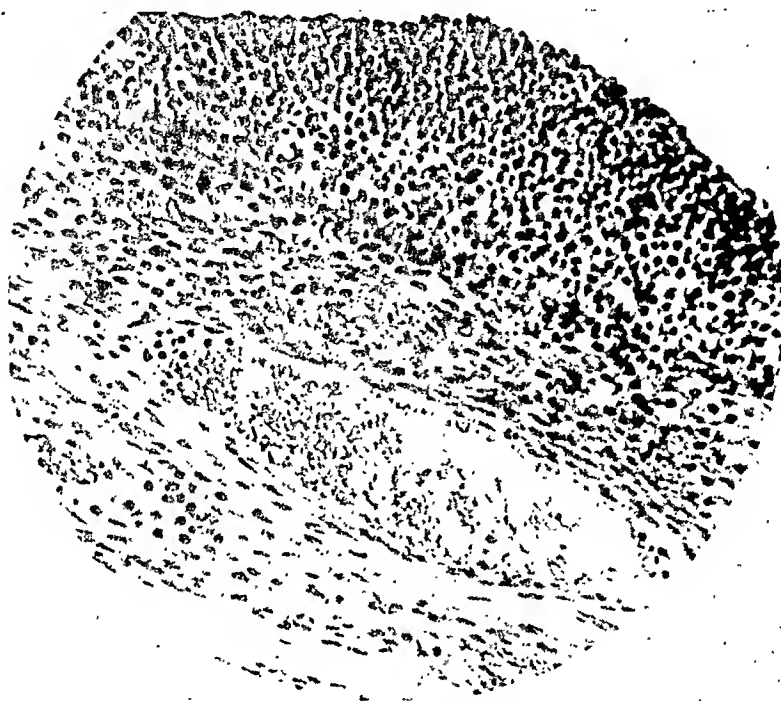


Fig. 8.—Case 15, right ovary. Early pseudoluteinization of the granulosa in a currently maturing follicle. Note the clarity of the granulosa cells near the theca interna. The theca interna cells show mutation from the spindle to the epithelioid to the ovoid form.

Such theca interna cysts could be told in the gross by their smooth, thin, yellow-tinted lining, and were encountered in 9 of 22 cases in this series. In older degenerated follicle cysts, the fibrous tissue mantle separating the hypertrophied theca-cell column from the cavity indicated reactivation of old theca cells. The number of adjacent capillaries was not increased but they were, however, often congested.

Corpora Lutea.—These were encountered in 14 cases as follows: corpus luteum of congestion, 4 cases; corpus luteum of vascularization, 5 cases; corpus luteum of efflorescence, 5 cases. All presented the morphology typical of their cyclic stages and corresponded to corpora of the current cycle. Multiple corpora lutea were frequent but were always of the same developmental age and form (Fig. 7). There were two instances of bilateral corpora lutea and three cases of multiple corpora in the same ovary. These findings are explained by hyperemia due to pressure stasis from the associated fibroids of the uterus. Geist, et al., also noted a high incidence of multiple corpora in their studies with chorionic gonadotropin.

Discussion

There are many clinical and experimental difficulties met in studies of equine gonadotropin. Since most patients in all series had fibromyomas of the

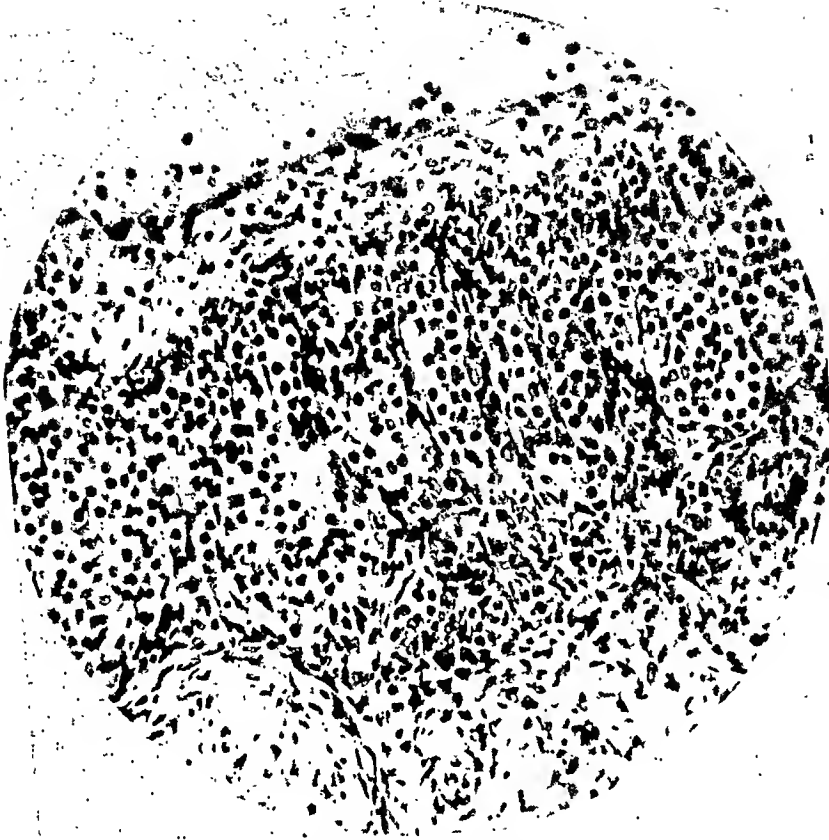


Fig. 9.—Case 8, left ovary. Theca interna cyst. Hypertrophy of the theca cells is pronounced. They are palisaded in columns defined by fibrous septa. The degenerating granulosa cells centrally line the cavity.

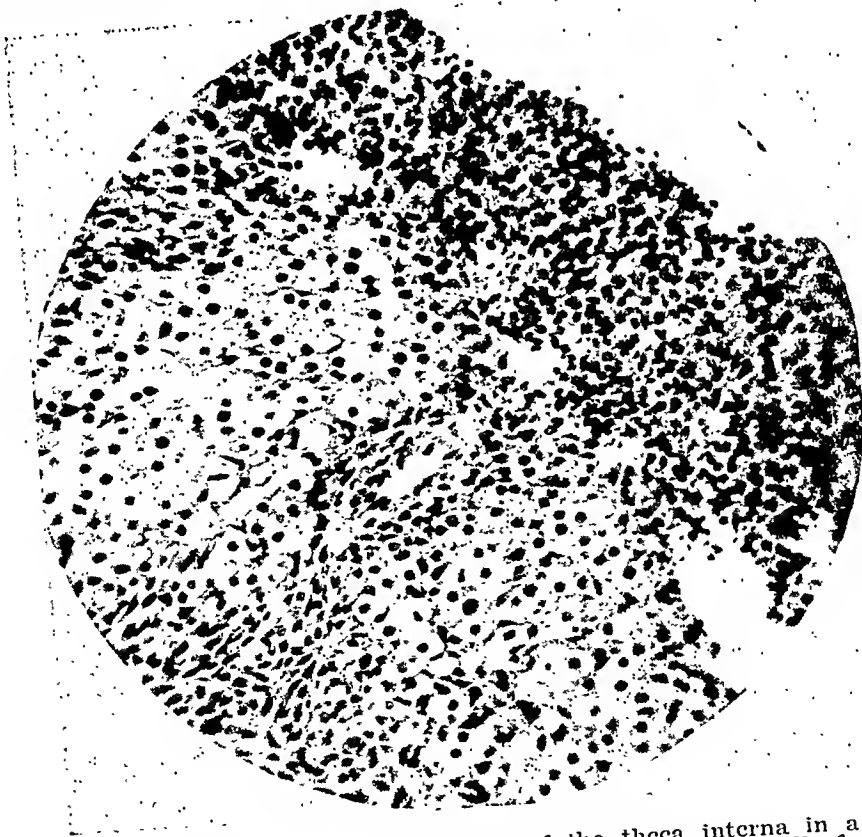


Fig. 10.—Case 15, left ovary. Hypertrophy of the theca interna in a recent follicle is most marked. Only the overlying granulosa layer differentiates theca cells from the true lutein type.

uterus, it must be indicated that large fibroids per se cause pelvic congestion, ultimately resulting in sclerocystic changes of the ovaries. How such organs respond to experimental stimuli is unknown. Ovaries of young women would appear most desirable for examination, yet radical surgery and removal of organs can only be practiced upon older patients. It is not unreasonable, however, to assume that gonads which ovulate and produce corpora lutea should be functionally receptive and morphologically responsive to stimulation by gonadotropic agents. Objections on an age basis, therefore, are not valid. The time of the cycle during which Gonadogen is given is of importance, for cyclic ovarian changes are occurring concurrently with those which may be induced by Gonadogen. Thus, in the midcycle, a recently ruptured follicle may be falsely ascribed to equine gonadotropin, and reversely, the actual rupture induced by use of this agent may be wrongly interpreted as normal to the cycle. The time factor becomes even more pertinent in the third week of the cycle when estrogen and progesterone secreted by the normal corpus inhibit the pituitary gland. A physiologic antagonist, therefore, is present which can interfere with stimulation by Gonadogen. In retrospect, studies with Gonadogen should have best been conducted immediately after the close of menses, at a time when normal inhibition to the pituitary by estrogen is in abeyance. Sequential observations are necessary for evaluation of functional or morphologic changes induced by Gonadogen but are not available in any plan of study presented to date. Positive proof of ovarian stimulation by gonadotropins requires evidence that more than the usual number of Graafian follicles are brought to maturation and ovulation or that the tempo of ripening in a solitary follicle is quickened. Basic knowledge in this direction is scant, for the number of primordial follicles which normally commence simultaneous maturation is not known. After ovulation has occurred from one, ova from contemporary follicles supposedly disintegrate. How long the discus proligerus surrounding such a degenerating ovum persists before the blighted follicle undergoes cystic atresia is not known. How then can the atretic follicle of the current cycle be distinguished from a persisting cystic follicle of the antecedent period?

In addition, the "pseudoluteinized" follicles of the current cycle (Figs. 3 and 4) which result from Gonadogen stimulation can be mistaken for a recently ruptured follicle with incipient corpus formation. However, the collapsed cavity of the normally ruptured follicle is more dentate, and a "punctum" is grossly observed. The early lutein cells, as already noted, are small, with scant acidophilic granular cytoplasm. The nucleus is small, round, and dark. The next change is elongation of the cell body, which later assumes a cylindrical form. Clear vacuolated cells are not seen until vascularization of the corpus is reached. This phase is easily identified in the gross by the large, measurable corpus presenting a gray-yellow lining enclosing a central coagulum, blood-tinged at the point of contact with the lutein cells. Once such differentiation is made, ovulation resulting from Gonadogen stimulation is excluded with certainty. In our study, ovulation was not established.

Conclusions

1. Experiments with equine gonadotropin (Gonadogen) as conducted in the human being are beset with numerous conflicting conditions, and binding conclusions are hardly warranted.

2. Such studies are best made in the immediate postmenstrual period when spontaneous maturation and ovulation have hardly begun.

3. Gonadogen does not cause orderly maturation of unusual numbers of Graafian follicles nor does it accelerate the tempo of maturation in follicles of a current cycle.

4. Although the primordial follicular unit is not stimulated, the granulosa layer is hypertrophic, due to increase in cell cytoplasm. In granulosa cells of a current follicle, the size and clarity of the cell simulate the lutein type and the term "pseudo luteinization" is warranted.

5. Hypertrophy and hyperplasia of the theca interna layer is the most marked Gonadogen effect. Reactivation in atresic follicles and even in corpora fibrosa occurs. Theca interna cysts are numerous.

6. Vascular engorgement is prominent and accounts for the hypertrophy of the granulosa and theca interna cells. Interstitial and intrafollicular bleeding is in frequent association.

7. The position of Gonadogen in the therapy of amenorrhea still remains problematic. It stimulates the granulosa and theca components of the maturing follicle or follicle cysts. There is no proof of inauguration of follicle maturation or rupture, induced by equine gonadotropin.

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CHOREA GRAVIDARUM

Review of the Recent Literature and Report of Five Cases

THOMAS W. McELIN, M.D., SIM B. LOVELADY, M.D., AND HENRY W. WOLTMAN,
M.D., ROCHESTER, MINN.

*(From the Section of Obstetrics and Gynecology, Mayo Foundation and Mayo Clinic, and the
Division of Neurology, Mayo Clinic)*

CHOREA gravidarum is an infrequent complication of pregnancy. Beck,¹ however, warned that though rarely observed it occasionally presents a grave problem. Ruch² suggested that the clinical picture which it presents is perhaps the most distressing of all the complications which the obstetrician encounters. The infrequent occurrence of this condition and the ominous portent which the diagnosis may convey warrant the presentation of five previously unreported cases. Moreover, to our knowledge, a consideration of the literature relevant to this problem has not been attempted since the monumental review of the subject by Willson and Preece³ in 1932. We have prepared a list of references of the articles which have appeared on this subject since that date and will consider briefly the conclusions of the American reports and of those available from the foreign literature.

Willson and Preece's article contained approximately 330 references from the world's literature to Sept. 30, 1930, and they submitted questionnaires to 530 members of obstetric societies throughout the United States inquiring whether or not these members had ever encountered this condition. From these data, the authors assembled with meticulous detail information concerning 951 choreic pregnancies occurring in 797 patients. A brief summary of the essential material from their communication will be presented. These data will serve as a convenient point of departure from which to consider the subsequent literature.

Survey of the Literature

Data from thirteen American hospitals suggested a hospital incidence of 1 case per 3,501 obstetric admissions. Extremes in incidence were 1 case of chorea among 146 pregnancies reported by Scott from Toronto and no case in 20,000 deliveries at the Dublin Rotunda. Willson and Preece suggested that the incidence in American hospitals gave an exaggerated concept of the frequency of this complication, since of 170 obstetricians replying to their questionnaire, 113 had never observed a case.

The average age of the patients was 22.4 years. Chorea associated with pregnancy was observed much more frequently in primigravid patients. An illegitimacy rate of 17.2 per cent was observed. The authors commented on the rarity of this complication in the Negro race.

A history of chorea unassociated with pregnancy was given by 48.1 per cent of the patients, and 12.8 per cent gave a history of chorea, the relationship of which to pregnancy was undetermined. Occurrence of previous episodes of chorea was denied by 39 per cent. A history of rheumatism was given by 35.3 per cent. Heart disease was noted in approximately one-third of the 797 patients. In approximately two-thirds of the pregnancies, there was a history of chorea or rheumatism or both. In sixty-eight cases of their series, some form of emotional disturbance preceded the attack. Pathologic data were admittedly incomplete, but of the forty-six cases in which necropsy was performed, cardiac pathologic change was observed in 86.9 per cent. Evidence of low-grade encephalitis was noted in some cases. Several investigators reported finding congestion and petechial hemorrhage and thrombosis in almost every part of the brain, such processes reaching a quantitative and qualitative maximum in the corpus striatum, especially in the caudate nucleus. The pathologic evidence as summarized in 1932 lent no support to the opinion that the toxemias of pregnancy have any etiological relationship to chorea gravidarum.

Half of the attacks were initiated in the first trimester, and a third in the second, and a sixth in the third trimester. In 529 pregnancies with nonfatal termination, the chorea ceased ante partum in 167, intra partum in one, and post partum in 361. In cases in which the patient died during pregnancy, the disease tended to run a shorter course. The average duration of those attacks terminating in recovery during pregnancy was about two and a half months.

The well-known symptom complex consists chiefly of hypermotility and incoordination, usually generalized. The movements usually cease during sleep. The patients are usually afebrile, and when fever does occur it is of ominous significance. Hyperpyrexia can occur.

The most frequent complications were stated to be acute psychosis, acute endocarditis, and rheumatic fever. Eclampsia occurred in six cases, in three cases chorea was complicated by hysteria, and in one, by epilepsy.

Encephalitis, pseudochorea, and pseudosclerosis were noted as entities to be considered in the differential diagnosis. Prior to the publication of Willson and Preece, mortality rates had run between 25 and 33 per cent. It was stated by these authors to be about 12.7 per cent from 1900 to 1932 in what they termed the "aseptic era in obstetrics," to differentiate this period from previous time intervals. A lower mortality rate was noted in cases of patients who had had chorea or rheumatism previously, and a still lower rate in those who had had both. Mortality rate appeared to have no relation to the month of pregnancy at onset. In cases in which spontaneous labor occurred at term, a mortality rate of 1.9 per cent was reported; in cases in which spontaneous premature labor occurred, 12.6 per cent; and in those in which spontaneous abortion occurred, 23 per cent. In a group of 171 cases in which pregnancy was terminated artificially, a mortality rate of 33.3 per cent was found.

The authors warned against the excessive use of depressant drugs. Sedation, adequate nourishment, rest, and general supportive measures were the common denominators of successful management. In cases of mild chorea, no reason for therapeutic abortion could be found. If intervention need be resorted to, Willson and Preece advised that the cases be selected carefully and that such interruption be by the induction of premature labor or abortion and not by immediate operative delivery except in rare instances, as the mortality rate for such procedures was about 50 per cent. The most reasonable indication for interference seemed to be progression of the chorea despite therapy, and they felt interruption should be carried out before infection occurs.

We were able to find thirty-three articles concerning chorea gravidarum from 1932 through December, 1946. A résumé of those available to us follows.

Guynes⁴ reported a case of fatal chorea gravidarum which developed in one week's time in the ninth month of gestation. The patient was a Mexican woman in her second pregnancy. The patient gave a history of mild chorea in the first pregnancy which was terminated by premature labor. In the pregnancy under consideration, labor and delivery were hastened by manual dilatation when the cervix was dilated to a diameter of about 5 cm. This procedure was resorted to because of the extremely serious condition of the patient. Cesarean section previously had been refused. Hyperpyrexia developed and the patient died on the second postpartum day. The authors concluded that it did not seem wise to temporize even in cases of apparently mild chorea complicating pregnancy in the later months. Hysteria, tic or habit spasm, epidemic encephalitis, senile chorea, Huntington's chorea, Friedreich's ataxia, and various intoxications were mentioned as entities to be considered in the differential diagnosis.

Kobrin⁵ presented a case of a 19-year-old, unmarried primipara who presented no evidence of cardiac disease. Chorea gravidarum developed in the sixth month of pregnancy and distinct improvement followed transfusion of 20 c.c. of blood from a healthy, pregnant woman. The author considered the chorea in his case to be of toxemic origin, as examination of the patient's urine showed heavy traces of albumin and granular casts, and edema of the ankles had been noted. The pregnancy was concluded in the eighth month after medical induction of labor. A normal female infant was born.

Brian and Gerundo⁶ reported a case in which they felt chorea was related to toxemia because of the nephrohepatic lesions found at necropsy. This patient, a secundigravida 35 years old, had not had albuminuria, edema, or hypertension in the prenatal period, as far as was known. The heart was normal. The patient was thought to have had acute cholecystic disease with icterus, a septic fever, and some vomiting in the fourth month of pregnancy. The authors in retrospect concluded that this might have been an episode of parenchymatous hepatitis. The chorea apparently began about one month before delivery. The patient was delivered of a dead fetus in what was probably the seventh month of gestation and died one month after delivery. The authors felt that the clinical course and the nephrohepatic lesions in this case could serve to distinguish chorea of rheumatic origin from that of toxemic origin. They felt that because hepatitis and possible pre-eclampsia preceded the chorea it was also of toxemic origin.

Weigner⁷ submitted a strong brief for the psychogenic origin of certain instances of gravidic chorea. In defense of this viewpoint he presented the following data: In 17 per cent of the cases the pregnancy was illegitimate. He stated that the peak occurrence was in the fifth month of gestation when quickening and other positive signs of pregnancy removed all doubt from the patient's mind as to the interpretation of the unwanted amenorrhea. He pointed out the fact that many cases have considerable psychogenic "color" and that patients in these cases were often cured by abortion or by dramatic and obviously nonspecific therapy such as sham abortion, cervical dilatation, incision of the hymen for the relief of dyspareunia or the removal of a urethral caruncle. Seventy cases from the literature were noted in which there were precipitating instances of an emotionally shocking nature such as fright, anger, a fall, or fire. Of 950 cases in the literature, some evidence of psychogenesis was mentioned in 137. In this particular group, the rheumatic background was mentioned in significantly fewer cases than in the cases in which evidence of psychogenesis was lacking. Weigner's conclusion was that chorea gravidarum should not be regarded as an entity but instead as an expression of a constitutional anlage which may be precipitated by various factors such as infection, toxemia, or psychogenic stimulation. The work of Gerty was mentioned. A report of a remarkable case was presented in which a striking psychogenic com-

ponent was evident. The chorea was terminated by suggesting in the presence of the patient that the pregnancy could be terminated were she to improve enough for such a procedure to be carried out. This patient previously had had chorea associated with tonsillitis. Development of chorea in response to both infection and psychogenic stimuli strengthened the ultimate conclusion that this phenomenon was a manifestation of a constitutional anlage. The term "choreiform behavior in pregnancy" was suggested as more precise than "chorea gravidarum."

Scheftel⁸ reviewed the literature to some extent and described the various hypotheses of etiology. She presented a case of a hysterical, mentally retarded woman who had hemichorea in her first pregnancy and presented a double mitral lesion. In the second pregnancy, chorea of a mild type recurred. In a third pregnancy, the chorea was generalized and moderately severe. The offspring had atypical Klippel-Feil syndrome.

Patterson⁹ reported a case of severe chorea in an unmarried girl, which he felt had been induced by the worry and shame caused by the pregnancy. Sodium Amytal appeared to have a definite beneficial effect but the bromides and morphine sulfate appeared to be of little value. Real improvement, however, did not occur until the pregnancy was terminated artificially. The past history was not given. No cardiac lesion was found. The temperature was normal. Surgical induction of labor was carried out at thirty-four weeks and the premature infant died fourteen hours after delivery.

Ruch² summarized many of the salient points of the recent literature and referred to chorea gravidarum as a rare disease. He reported a single case. The patient was the wife of a medical student. Chorea developed in the fourth month of gestation. No clinical history of rheumatic fever was obtained nor was there a demonstrable cardiac lesion. However, intermittent low-grade fever was present and a polyarthritic episode occurred after therapeutic emptying of the uterus by cesarean section in the sixth month. Ruch quoted Royston to the effect that if a choreic patient becomes pregnant the prognosis is not necessarily serious, whereas if chorea appears for the first time after conception, it is always of grave import and failure to distinguish between these two situations probably explains the marked variations in mortality figures. DeLee¹⁰ is quoted regarding the occasional cases of chorea associated with fetal abnormalities and the statement was made that such abnormalities often are confined to the head and spinal column. Ruch stated that the left side of the body is more commonly involved and that personality changes often are noted. Involvement may vary from mild twitching in an isolated muscle group to generalized disability causing impairment or total loss of powers of speech and deglutition often necessitating forceful restraint. In the majority of cases the chorea is mild. In cases of severe chorea, Ruch advised termination of pregnancy—the sooner done the better—and stated that delay invites a higher mortality. Abortion is regarded as the procedure of choice, although cesarean section is usually preferable if the pregnancy is well advanced and the choreiform movements become violent. Fever is listed as an added indication for intervention.

The foreign literature, like the English literature, has consisted mostly of reports of single cases.

Dražančić¹¹ emphasized his mode of treatment of a primipara in the fifth month of pregnancy. The patient was given twelve subcutaneous injections of peptone and improved after the first treatment. The author was of the opinion that he was the first to have attempted this form of treatment. The patient lived and the child died of unknown cause on the sixth postnatal day. The author concluded that chorea associated with pregnancy was neither neurogenic

nor infectious but was allergic in origin. He felt that the allergenic factor might be a protein stemming from the fetus and hence used the peptone as a desensitizing agent.

Nordmeyer¹² favored a toxic etiology as most likely in severe chorea gravidarum and reported a case in which a definite rheumatic background, cardiac signs, albuminuria, and normal blood pressure were noted. He obtained a favorable result with cesarean section and stated that this procedure should be carried out when the condition is severe.

Thiele^{13, 14} reported twenty-one cases which had been encountered in twenty years with one death. Döderlein¹⁵ reported seven cases.

Levy-Valensi and his colleagues^{16, 17} presented a case in which evidence of toxemia was not found and a previous history of chorea was obtained. The patient died as the result of rheumatic endocarditis. These authors were particularly interested in the concentration of lactic acid in the blood, and on the day of their patient's death the concentration was the greatest they had ever encountered. They postulated that the chorea plus the cardiac decompensation in their case might have produced such a level.

Laffont and Castanier¹⁸ had a secundigravida patient whose first child had had hydrocephalus. Chorea gravidarum developed during the second pregnancy and the patient died. A sister had died of a postpartum psychosis. Their patient had a normal blood pressure and no albuminuria. Necropsy was not performed.

Brémond¹⁹ described a case of chorea in a primiparous patient who was delivered of a normal baby. The patient had received conservative therapy. She had severe vomiting associated with the pregnancy.

Gosende and Sandiano²⁰ reported a case in which they believed the chorea to have been caused by "the toxins of pregnancy." Dutra²¹ and Rabin and Duck²² described three cases in which cure was effected by pyridoxine (Vitamin B₆) therapy.

Review of the discussions concerning chorea gravidarum in modern textbooks on obstetrics provided the following:

Titus²³ recommended the use of barbiturates in moderately large doses. He also suggested the removal of foci of infection, keeping the patient at absolute rest in bed, use of a high carbohydrate diet, and the parenteral administration of a hypertonic solution of glucose to compensate for excessive glycogen consumption by constantly jerking muscles.

Beck¹ emphasized rest in bed, isolation, careful feeding, and the use of sedative drugs as therapeutic measures. He further suggested that intravenous injection of a solution of magnesium sulfate often has a quieting effect when other sedatives fail. Improvement after the use of arsphenamine has been noted.

Irving²⁴ emphasized the seriousness of prognosis if chorea occurs for the first time during pregnancy and gave the mortality rate as 18 per cent. If it occurred in a previous pregnancy, the rate is about 10 per cent and if the chorea of pregnancy represents a recrudescence of adolescent chorea the mortality rate is about 7 per cent. He stated that about 25 per cent of women who have chorea during adolescence have a recurrence during pregnancy. In the presence of fever, the mortality rate is said to be about 70 per cent.

Stander²⁵ quoted Wilson whose opinion was that induction of abortion is unnecessary in cases of mild chorea and does no good when the condition is severe. Twelve cases in 34,569 pregnancies were encountered at New York Lying-In Hospital.